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Proceedings of the Fifteenth BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

CARDIFF, 14th–16th JULY, 1959

Editor of Transactions: JAMES G. LAWSON

SCIENTIFIC PROGRAMME

Tuesday, 14th July, 1959

Morning Session

Chairman: Emeritus Professor G. I. STRACHAN, President

The Congress opened by Sir William Fletcher Shaw, Manchester

A SYMPOSIUM

REMOTE EFFECTS OF OBSTETRICAL HAZARDS ON THE DEVELOPMENT OF THE CHILD

Guest Opening Speaker: Dr. DUNCAN E. REID, Boston

Invited Speakers: Dr. C. M. DRILLIEN, Edinburgh, Dr. HILDA KNOBLOCH, Columbus, Ohio and Professor G. SHEDDEN ADAM, Brisbane

Discussion on the Hazard of Prematurity

Afternoon Session

Chairman: Dr. J. BRUCE DEWAR, Dumfries
President of the Edinburgh Obstetrical Society

SYMPOSIUM ON OBSTETRICAL HAZARDS (*continued*)

Invited Speakers: Sir DUGALD BAIRD, Aberdeen, Dr. ALICE STEWART, Oxford, Dr. MARK S. FRASER, Aberdeen, Dr. B. PASAMANICK, Columbus, Ohio and Professor J. WALKER, Dundee

Wednesday, 15th July, 1959

Morning Session

Chairman: Mr. W. R. SLOAN, Belfast

President of the Ulster Obstetrical and Gynaecological Society

PSYCHOSOMATIC GYNAECOLOGY

Invited Speakers: Dr. DESMOND O'NEILL, London, Mr. ALECK BOURNE, London, Dr. J. W. JOHNSTONE, Melbourne, Dr. HOWARD TAYLOR, New York and Dr. ELINOR BLACK, Winnipeg

Afternoon Session

Chairman: Mr. H. AGAR, Leeds

President of the North of England Obstetrical and Gynaecological Society

OESTROGEN METABOLISM

Invited Speakers: Sir CHARLES DODDS, London, Dr. J. B. BROWN, Edinburgh, Professor ROBERT KELLAR, Edinburgh and Dr. G. I. M. SWYER, London

Thursday, 16th July, 1959

Morning Session

Chairman: Professor H. J. DREW SMYTHE, Bristol

Vice-President of the South West of England Obstetrical and Gynaecological Society

Guest Lecture: Dr. HOWARD TAYLOR, New York

STUDIES IN THE CLINICAL AND BIOLOGICAL EVOLUTION OF ADENOCARCINOMA OF THE OVARY

THE CONTRIBUTION OF RADIOTHERAPY TO THE MODERN TREATMENT OF MALIGNANT DISEASE OF THE FEMALE GENITAL TRACT

Invited Speakers: Dr. W. G. COSBIE, Toronto, Professor B. W. WINDEYER, London, Mr. C. J. L. THURGAR, Newcastle-upon-Tyne, Mr. S. A. WAY, Newcastle-upon-Tyne and Dr. I. CHURCHILL-DAVIDSON, London

Afternoon Session

Chairman: Mr. S. DAVIDSON, Birmingham

President of the Birmingham and Midland Obstetrical and Gynaecological Society

THE PLACE OF OXYTOCIC DRUGS BEFORE THE BIRTH OF THE CHILD

Invited Speakers: Mr. A. J. WRIGLEY, London, Professor J. CHASSAR MOIR, Oxford and Mr. G. W. THEOBALD, Bradford

OPENING OF CONGRESS

BY

SIR WILLIAM FLETCHER SHAW

MY first reaction to the unexpected and flattering invitation to open this Congress was that this was a new departure and that one so long retired from practice as myself was not a suitable choice. You, Mr. President, corrected my faulty memory, reminding me that the last three Congresses had been formally opened and still very kindly pressed me to perform this ceremony, though you took the precaution, always a wise one when dealing with the elderly, to instruct me not to speak for more than 10 to 15 minutes.

I found from the records that the last three Congresses were officially opened but in each case by one holding such high office that it seemed only natural he should be present to say a few words of welcome and I had not thought of them as official openings; in London the Minister of Health, in Leeds the President of the Royal College of Obstetricians and Gynaecologists and in Oxford the Vice-Chancellor of the University. I hold no high office nor in fact any office, high or low, and I assume I am chosen because I am one of the very few now surviving—I can only recall 3 others—who were present at the first meetings which, gradually increasing in size, developed into this great Congress.

The first was in 1911, forty-eight years ago. In that year the Glasgow Obstetrical and Gynaecological Society celebrated its Silver Jubilee and to mark the festivities invited the North of England Obstetrical and Gynaecological Society, which that year came of age, to visit Glasgow for two to three days. This wholesale invitation in itself demonstrates the great development during the last two decades.

In those far off days, consultants were limited almost entirely to University Centres and were few in number. The North of England Society which met alternately in Liverpool, Manchester, Leeds and Sheffield, probably had an active membership of not more than 30, so we were invited as a body and each was entertained in the home of one of our Glasgow hosts. We had a most hospitable and enjoyable time, so much so that two years later, in 1913, the North of England Society desired to return the hospitality and, as it was the turn of Manchester to nominate the President and Secretary, the meetings were held in that city. I find from the records that the Edinburgh and Midland Societies were invited as well as the Glasgow Society and, unless my memory is at fault, also some friends from London, though these may have been invited individually as the London Society is not mentioned in the record.

In 1920, when things were settling down after the first world war, the Obstetrical and Gynaecological Section of the Royal Society of Medicine staged a meeting in London to which they invited the North of England and the Midland Societies. From the record these appear to be the only societies invited though the opening paper was given by a Dublin obstetrician, Dr. Hastings Tweedy, while Professor MacKerron of Aberdeen and Professor Munro Kerr of Glasgow took part in the discussion. So successful was this meeting that it was then and there decided to repeat it annually and to call it the British Congress of Obstetrics and Gynaecology, the first to be in Birmingham the following year, 1921. This also was very successful as was the next one in Liverpool in the following year, 1922.

In the reports of these meetings the Birmingham Meeting in 1921 is correctly described as the first Congress while the Liverpool Meeting in the following year, 1922, is called the third Congress which suggests that someone wished the London Meeting in 1920 to

rank as the first Congress. Since then these Congresses have been held regularly, at first annually, then bi-annually, and more recently, tri-annually. It was at the fifth Congress in London in 1925 that overseas guests are first recorded in the person of Whitridge Williams of Baltimore.

Now why do people come to Congresses? The papers read at this and any other Congress later appear in one of the Journals and can be read in comfort in our own studies without the trouble and expense of travelling. The answer can only be to meet and assess each other by personal contact and friendly discussion between the formal meetings.

It is one thing to read a paper by a complete stranger; quite another by one we know and respect. If a paper by a complete stranger disagrees with our preconceived ideas on our pet subject, we are less likely to give it that complete consideration which we would if the writer was one we had met personally and had assessed as thoroughly trustworthy. How often a stranger whose writings have ruffled our feelings turns out on acquaintance to be a pleasant, modest and thoroughly reliable man and how often we review our own opinions after such a meeting. Knowledge from personal contact is so much more reliable than from reading alone.

Then again how many lasting friendships, which add so much to our pleasure in life, originate at these meetings; not only from amongst our own countrymen but from visitors from overseas. Looking back over the years I am grateful for the many friendships made in the first instance in these or similar meetings and later fostered by correspondence and frequently by exchange of hospitality in each other's homes, so that many of them, widely separated though we were and meeting only occasionally in the flesh, nevertheless were counted amongst my dearest friends.

Even though I may be exceeding my allotted time, I cannot close without expressing my great pleasure to be here under your Presidency, Mr. President. Nothing else would have brought me out of my retirement. We have been friends for very many years and worked closely together to found our College, in fact the proposal to found the College was first put forward at a meeting of the Gynaecological Visiting Society in this City in 1924. It is therefore a great joy to sit under your Presidency of what, we are all sure, will be an outstanding Congress. In declaring this Congress open, the best wish I can have for all the members, especially the younger ones with so many years before them, is that they may be equally blessed in the friendships commenced at this Congress.

REMOTE EFFECTS OF OBSTETRICAL HAZARDS ON THE DEVELOPMENT OF THE CHILD

A Review of the Problem

BY

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INTRODUCTION

IT has been a hallmark of those responsible for the care of the parturient and the newborn to review periodically and discuss current problems. A free discussion of carefully considered opinion of patient management usually results in improved patient care.

Except by those engaged in the problem, it is not generally appreciated that the greatest risk to survival during an individual's lifetime is encountered in the perinatal period. Until very recent times Medicine has devoted most of its energies toward an understanding of Man's extra-uterine existence and has given much less attention to his intra-uterine environment. An analysis of trends in research during the past decade indicates an awakening of interest in this process upon which the future of mankind depends. The topic selected for discussion today reflects this interest.

Purposely it is an all-inclusive subject; although this imposes certain difficulties in selecting from a large number of items those which appear controversial, important, and of general interest, it also permits establishing lines of communication between the various groups who have as their purpose a common goal. This not only serves to promote ideas and speculation, but it creates an awareness of the proposed question in its entirety.

As my assignment I have made an attempt to define the problem from two points of view, namely perinatal morbidity only as it relates to its remote effects on the child, and congenital defects. With respect to congenital defects it is proposed to discuss briefly environmental versus genetic factors of aetiology, irradiation hazards in obstetric practice, and to raise the question of therapeutic abortion in reducing the incidence of severe congenital malformations. Perinatal morbidity will be considered under topics dealing with assessment of the foetus *in utero* and the newborn at birth, and some of the more common obstetric complications believed to contribute to disabling conditions in the individual. The question of premature delivery is one that will be dealt with by other panellists who are more familiar with the problem. In fact, prematurity is a vast problem in itself, being concerned in most instances with factors which control the reproductive process of which we know so little.

THE PROBLEM AND ITS AETIOLOGICAL FACTORS

The problem under discussion is whether and under what set of circumstances prenatal and perinatal patho-physiological states cause mental and physical defects in the child. These range from serious physical malformations and other

equally major conditions of cerebral palsy, epilepsy, and mental retardation to less serious but much more frequent situations of difficulties in speech, the learning process, and deviations in behaviour.

The advances in surgical and medical care permit a greater number of individuals with congenital defects to survive and, as Ingram (1955), Ellis (1958), Drillien (1958) and others have emphasized, the same applies to cerebral palsy and other associated disorders. An example is the careful studies by Drillien (1958), who has given further, if not conclusive, evidence that emotional disorders and mental retardation are commonplace among low weight infants who survive. Cerebral palsy and allied conditions are no respecters of families, for their incidence is apparently not appreciably influenced by social, economic or cultural factors, except as they possibly affect the incidence of prematurity.

Kurland (1957) suggests that cerebral palsy be narrowed to those disorders of uncertain and unknown aetiology arising during pregnancy and the perinatal period and affecting the motor function of the brain, the resultant dysfunction being recognized prior to the end of infancy (2 years). In a careful study in Rochester, Minnesota, reported by this author, the prevalence rate was 1·6 per 1,000 population under 20 years of age. In another regional study in the United States, Levin and associates (1949) found that a considerable number of youngsters afflicted with cerebral palsy die within the first five years. Also, a high proportion of patients with the disease are undiagnosed up to this time, and certainly the diagnosis is difficult before the age of one year. This may account for the large differences in the reported incidence of cerebral palsy. Finally, in the patients under the age of twelve studied by Levin, 90 per cent or more apparently acquired the disease at birth, meningo-encephalitis or extra-uterine trauma playing a small role in this age group.

Recognizing the deficiencies in case finding and differences in defining cerebral palsy, one is forced to conclude that it occurs less often in Britain and the Scandinavian countries than in the United States and Canada, where the reported incidence is 2–6 cases per 1,000 adult population. Difficulties with learning, and speech and behaviour deviations perhaps should also be included, making the problem even more formidable.

In considering the aetiology of these conditions we must begin with the classical paper of the orthopaedist, Dr. W. J. Little (1862) who, on observing 200 cases of spastic rigidity, was convinced that they could be traced to causes surrounding birth. Dr. Little states: "The new born child . . . tolerates a longer duration of suspended animation . . . asphyxia neonatorum . . . than the adult. Yet, the delay of only a few moments would lead to the apprehension that even the want of a few breathings, if not fatal to the economy, may imprint a lasting injury on it." Further he expressed the belief that unnatural presentations, tedious labour from rigidity of maternal passages or apertures, and instrumental delivery as well as turning procedures, premature labour, entanglements and prolapse of the cord, and a lack of or improper attention to the newborn furnished the background for certain subsequent mental and physical derangements of the child.

With the present-day realization that birth injury is primarily one of intra-uterine asphyxia rather than trauma, the aetiological factors can be reclassified in various ways as they may contribute to hypoxic states in the foetus and newborn.

The following arbitrary classification is appended:

(1) A decrease in the rate and the amount of foetal-placental blood flow through cord compression.

(2) A decrease in the maternal placental flow of blood (intervillous space), due to hypotension as with spinal anaesthesia, arrest of the blood flow as with tetanic contraction and the increasing uterine tonus in prolonged labour, the improper use of oxytocic drugs, or disruption of the integrity of the intervillous space as in abruptio placentae or placenta praevia.

(3) A decrease in the exchange of respiratory gases across the trophoblastic membrane. Fibrinoid deposition, placental infarction and ageing, etc., must be considered as possibly causing a reduction in gaseous

exchange. It has long been recognized that infants die *in utero* in pregnancy toxaemia, due as much perhaps to an interference with placental membrane exchange as to a critical reduction in the rate of intervillous blood flow.

(4) A decrease in the maternal alveolar exchange of respiratory gases. This apparently must be extreme before it affects the foetus. In fact, in severe cardiac failure or in beryllium poisoning, the foetus is not harmed, despite the reduction in the rate of maternal blood flow or the decrease in the arterial saturation of the maternal blood.

It is suggested, at least for clinical purposes, that intra-uterine asphyxia be classified into either acute or chronic forms. In the latter there would be such conditions as pregnancy toxaemia, perhaps diabetes and postmaturity or, in short, placental insufficiency. There is the impression that if infants from these mothers survive, rarely do they show central nervous system damage. By contrast, infants delivered under acute episodes of anoxia are more likely to show sequelae. These are cases of late pregnancy bleeding or where foetal distress develops in the course of labour and delivery, especially with compression of the cord. In the case of chronic asphyxia the foetus, as suggested by Walker (1954), may have an opportunity to marshal its physiological forces sufficiently to maintain the metabolic integrity of the tissues when they are unable to obtain their normal complement of oxygen.

Before dismissing the subject of aetiological factors which might cause remote effects on the child, some mention must be made of the influence of kernicterus which may develop from causes other than Rhesus and ABO incompatibility. Hyperbilirubinaemia seemingly is being encountered with increasing frequency and for reasons which are not clear. Apparently it is more than simply an increased awareness of its importance, or that it is being searched for with greater diligence by both the physician and the nursing personnel. Although it may develop in the course of infection, some authorities have questioned whether hyperbilirubinaemia may on occasion be iatrogenic in origin, due perchance to medications given the mother during pregnancy or to the infant at the time of birth. Because of its ability experimentally to produce icterus, the question has been raised whether vitamin K should continue to be used, and, if so, in what dosage. It is perhaps well to recall the well-accepted relationship between the prolonged use of high concentrations of oxygen commonly administered in the management of the premature infant and the production of retrolental fibroplasia. All forms of therapy given to the mother during pregnancy and labour should be under constant surveillance as to the possibility of creating an adverse effect on the foetus and newborn.

Despite extensive investigations into the production of various malformations by different teratogenic agents, the aetiology of congenital defects in the human is largely unknown. In fact, whether the experimental agent be irradiation, anoxia, nutritional deficiency or viral infection, congenital defects apparently appear only after a relatively prodigious insult to the conceptus.

The situation is further complicated by the fact that the comparative influence of genetic and environmental factors in the aetiology of malformations has been difficult to delineate. Rather than remain a hypothesis, oft-times conclusions have been drawn based on unsound evidence. This is perhaps best illustrated in mongolism, where the generally held view has been that the condition is attributable to environmental disturbances. Ingalls (1947) has held that the causative agents are numerous, including threatened abortion, pathological abnormalities of the uterus and certain acute intercurrent infections. As every obstetrician appreciates, vaginal bleeding in the early weeks of pregnancy, a time when mongolism is believed to begin, is common; in fact, it occurs in 15 to 20 per cent of pregnancies. The extreme rarity of mongolism is difficult to relate to the frequency of early pregnancy staining. It has now been shown by British workers (Jacobs *et al.*, 1959) that there is a genetic origin, at least the condition is associated with an extra chromosome.

While many viruses are suspected, only the virus of rubella can be implicated in causing the

development of a grossly defective child. There can be no doubt that severe malformations of the cardiovascular and central nervous systems, including microcephaly, may result if the mother has rubella during the period of organogenesis, but there is some doubt as to the exact incidence of these malformations. More recent evidence seems to indicate that some 15–20 per cent of patients who acquire the disease during the first eight weeks of pregnancy will deliver infants with marked physical and mental deficiencies. Consequently, it is the policy of our clinic to consider therapeutic termination of pregnancy in mothers who contract rubella in this period of gestation.

It is reasonable to suppose that malnutrition of the mother may have an adverse effect on the growth and development of the embryo and foetus. In the experimental animal, foetal teratogenic effects have occurred through lack of riboflavin, vitamins A and E, and pantothenic and pteroylglutamic acids, and foetal abnormalities have resulted when the maternal stores were depleted of these essential nutrients. There is no proof, however, that a state of malnutrition causes abnormalities in the human foetus. Actually, should a malnutrition exist in the human female to the degree that was produced in the experimental animal, conception would probably not occur due to the resultant upset in the pituitary-ovarian function. Certainly in times of famine a relative state of infertility exists among the female population, for amenorrhoea is the rule.

With the arrival of the atomic age, the potential hazards of ionizing radiation on biological processes have assumed greater significance and rightful concern. This is particularly pertinent to the biology of pregnancy, for radiation decreases reproductive capacity and causes genetic mutations. Further, foetal tissue is regarded as more sensitive to irradiation. The problem is concerned with both immediate and truly remote effects but it is also twofold. Specifically, the immediate effect relates to the aetiology of malignant disease, more particularly leukaemia, and the remote to the mutation rate. Certainly, such serious consequences must receive the thoughtful attention of those responsible for the care of pregnant women.

The anxiety regarding the hazard of X-ray exposure places the obstetrician in a rather untenable position, for to the biologist and geneticist any amount of irradiation during pregnancy is too much. Where indicated, however, X-ray examination of the chest by the conventional five-metre plate and pyelography restricted to 2 or 3 plates (the foetus being appropriately screened) are probably quite justified. It is admitted that the skin test for tuberculosis is less accurate during pregnancy. Further, conditions in the chest other than tuberculosis may be initially identified by X-ray examination (such as an anomalous condition, cardiac enlargement, tumours, etc.). It seems reasonable to suggest that pelvimetry examination is permissible on sound indication but, if possible, the procedure should never be repeated. Certainly opinions vary as to which method of X-ray pelvimetry is the most valuable. It follows that the profession should decide not only on what types of X-ray examination can be safely done during pregnancy, but also the technique to be used. Finally, if X-ray pelvimetry should be postponed until the last weeks of pregnancy, irradiation to the foetal gonads (except for breech presentation) can be avoided. Like other medical decisions, balanced clinical judgment is needed when X-ray examination is contemplated during pregnancy.

Late pregnancy bleeding is mentioned to emphasize the perplexing problems of immediate and remote foetal risk in overall patient management. In recent years, particularly through the influence of Macafee of Belfast, there has been a greater tendency to treat patients suspected of having a placenta praevia expectantly, at least until the last five weeks of pregnancy. The objective of this policy is laudable, for it hopes to postpone obstetrical interference until the foetus attains a state of maturity sufficient to ensure its survival. There seems to be no doubt that premature infants from mothers who experience bleeding in late pregnancy have a higher perinatal mortality and morbidity than a comparable group from mothers, with, for example, toxaemia or other metabolic disorders. Therefore, delaying delivery in ante-partum haemorrhage cases until near term is the preferable management. At the same

time, the question can be asked whether recurrent bleeding increases the hazard of irreversible asphyxia in the foetus. The opinion has been gradually formed in this clinic that the foetus is less likely to develop respiratory distress in the neonatal period if delivery can be postponed for several hours or days from the time of the bleeding episode. An immediate Caesarean section may accentuate rather than alleviate the hypoxial effect on the foetus created by disruption of the intervillous space and diminished intervillous blood flow. This applies particularly to patients where the baby is of borderline maturity.

Assessment of the Condition of the Foetus

The obstetrician as well as others who must cope with such matters would like to know how much asphyxia the foetus can endure and survive, or survive and escape irreversible damage to its central nervous system. In the present state of knowledge the status of the function of the foetal heart is the only gauge of the condition of the foetus *in utero*. In the clinical evaluation of what constitutes foetal embarrassment, Hon (1959), in his electrocardiographic studies of the foetal heart rate in labour, confirms the impression that physiological bradycardia may occur from pressure on the foetal skull, often encountered as the vertex transverses the inlet, particularly when the occiput comes in contact with the sacral promontory, as in an occipito-posterior position. Severe foetal bradycardia and irregularity were noted in maternal syncope, hypotensive states with caudal anaesthesia, and with frequently occurring strong uterine contractions. Hon believes that foetal bradycardia with tumultuous labour or maternal hypotension is more serious than transient umbilical cord compression and, further, that a bradycardia which begins toward the end of the contraction is more ominous than a bradycardia confined to the contraction period.

According to Southern (1957), no variations were noted in the electrocardiograms in the presence of pregnancy toxaemia and hypertensive disease, suggesting that the method is not applicable for predicting possible death *in utero*, a threat in these conditions which every clinician fears. Refinement of present techniques or methods other than recording of the foetal heart are necessary to anticipate hypoxia if death *in utero* or irreversible foetal damage is to be averted.

Assessment of the Infant at Birth

A number of physiological and clinical observations have been suggested for the evaluation of the physical state of the infant at birth, to ascertain to what degree the infant is depressed either from an oxygen deficit, the effects of analgesic and anaesthetic agents, or injury to its respiratory centre. Certainly the obstetrician and the paediatrician both appreciate fully how difficult it is to identify and separate these major causes one from the other in a given infant at the time of birth and in the early days of life.

Considerable weight has been placed on the oxygen content of the cord blood obtained at birth, with comparisons being made between the values obtained in normal and abnormal states. A body of such data is now available, but definite limitations are imposed by the various techniques of collection so that a degree of caution must be exercised in interpretation.

Although umbilical blood with a normal oxygen value at birth may mean a well-oxygenated newborn, Apgar and her associates (1955) have shown that the foetus in many instances is vigorous and not depressed when the umbilical arterial blood is 10 per cent or less saturated. They were forced to conclude that oxygen values alone are not a reliable index of the clinical state of the infant at birth.

Much has been made of the fact that the oxygen content of the cord blood is often low in babies born to mothers with toxaemia, prolonged labour and perhaps postmaturity. But if the value of the oxygen content of the cord blood is meaningful, the rate of umbilical blood flow should also be known, data which are obtainable only under special circumstances where the cord can be exposed without disturbing the pregnancy, such as at the time of Caesarean section. In other words, it is possible that the oxygen content of the umbilical vein may

be normal but the blood flow through the cord markedly impeded and the foetus in oxygen deficit.

Despite the fact that Bancroft-Livingston and associates (1958); Macafee and Bancroft-Livingston (1958) and others have not been able to confirm Walker and Turnbull's (1953) contention that prolongation of pregnancy is associated with hypoxia and alterations in the concentration and proportions of foetal and adult haemoglobin, perhaps the foetus employs more subtle mechanisms to ensure its survival in an unfavourable environment. Could it be that the foetus may utilize the anaerobic component of its metabolism when needed, which Huckabee (1955) has recently shown occurs in the adult who is in acute heart failure?

Villee (1959), an authority on the biochemical features of the foetus, concludes that: "the remarkable resistance of the mature foetus to hypoxia is not the result of some single metabolic change, but is the result of a combination of several, perhaps many, alterations in the metabolic patterns, each of which adds a small amount to the energy economy of the foetus. Added together these metabolic adaptations provide a considerable measure of safety to the foetus as it undergoes the birth process."

It is evident that chemical determinations on the cord blood have limited value and are beyond the reach of routine clinical practicability as a method of assessing the physical state of the infant at birth. Rather, the clinician must still depend upon certain physical signs and symptoms which the foetus exhibits at delivery.

Of the several ways of evaluating the physical status of the infant at birth, the scoring system of Apgar is gaining wide popularity. According to Apgar and associates (1955), the heart rate and respiratory effort are more important than the muscle tone and reflex irritability, and the infant's colour least important of all. Deterioration of the infant is accompanied by a fall in heart rate and decreased irritability.

Such an evaluation may have several purposes, including assessing the various means of resuscitation. More particularly, the main purpose is to try and relate the obstetrical complications and practices and the condition of the infant at birth with the presence or absence of central nervous system damage in his subsequent growth and development.

This method of assessing the infant has been incorporated in the Collaborative Study concerned with cerebral palsy and allied disturbances which is being sponsored by the National Institute of Neurological Diseases and Blindness of the United States Public Health Service and in which our institution is a participant. Prior to the initiation of this programme, however, a study was under way at the Boston Lying-in Hospital, the purpose of which was to evaluate the various recommended resuscitative measures and the circumstances under which they might prove particularly helpful. To enhance its objectivity, rather than the obstetrician scoring the newborn in accordance with the Apgar method, the observations were made and collected by a group of paediatricians under the direction of Dr. Clement A. Smith. Their preliminary findings suggest that Apgar scoring failed to offer an immediate prognosis as to survival or death. These infants have been followed for only a short period, and it is much too soon to know whether the Apgar method of scoring is valid in relating the state of the baby at birth with the subsequent state of its central nervous system.

Finally in the assessment of the infant at birth is the question of the presence of infection which has both immediate and remote connotations. It is now appreciated that hyperbilirubinaemia resulting from infection may produce irreversible damage of the central nervous system in the form of kernicterus. Thus, the obstetrician is concerned not only with the prevention of infection during labour, but, together with the paediatrician, in its early recognition in the newborn.

The usual signs of leukocytosis and fever are frequently not present in the newborn with infection, and consequently the condition is not always suspected and, indeed, is too often first diagnosed at autopsy. Drs. Benirschke and Clifford (1959) of our clinic have devised a simple technique whereby, with a frozen section of the cord secured at delivery, a diagnosis of umbilical vasculitis may be made or excluded in a matter of minutes after birth. The incidence

of vasculitis in consecutive cases was found to be about 10 per cent, which surprisingly and interestingly included many patients where the membranes were intact and labour normal. Such are the vagaries of intra-uterine infection. Early diagnosis and treatment are obviously important, including in some instances exchange transfusion to combat a haemolytic effect of the infection. Although the babies with a positive cord are suspected of infection, treatment is withheld until there are other clinical findings to support the diagnosis.

The Avoidance of Birth Trauma

In the evolutionary process, birth in the human female has become more difficult than in other primates because of changes in the architecture of the bony pelvis. In the sub-human primate the pubic arch flares widely and, consequently, with birth the perineum is permitted to dilate uniformly. The sacrum, moreover, ends at the inlet and the ischial spines are barely present, so that whatever bony obstruction occurs is restricted to the superior strait. By contrast, the human female must deliver a foetus with a comparatively larger vertex through a mid-pelvic plane which is confined by a sacrum, the ischial spines, and an outlet with a pubic arch that permits only the posterior component of the perineum to dilate.

In overcoming these obstacles difficult forceps operations with their hazard of both maternal and foetal trauma are performed less frequently than heretofore, and rightly so. This is acceptable by making Caesarean section a safer procedure by improved anaesthesia and the availability of antibiotics. Further, the classical X-ray studies of Caldwell, Thoms, Moir, and their colleagues of the architecture of the female pelvis have made the clinical examination of the obstetrical pelvis more meaningful and the forceps operation a more scientific procedure. In the writer's opinion, there are at least three anatomical features of the obstetric pelvis observed by Caldwell and others that have not received the attention they deserve in the avoidance of trauma at birth and facilitating delivery in the already asphyxiated infant. Firstly, Caldwell and his associates (1935) have proposed that the pelvic axis is not continuous, but rather is two separate entities. The superior axis originates at the intersection of the transverse and antero-posterior diameters of the inlet and descends downward parallel to the sacrum, ending at the sacrococcygeal area, or what Caldwell chooses to call the "sacrococcygeal platform". The inferior axis of the forepelvis begins at the centre of the anterior sagittal diameter of the inlet and descends parallel to the posterior surface of the symphysis, emerging at or slightly anterior to the centre of the transverse diameter of the outlet. Only the portion which lies at or below the level of the ischial spines, however, is utilized by the foetal vertex (Fig. 1).

According to this concept of the location and direction of the pelvic axis, the vertex in its course through the upper pelvis descends parallel to the sacrum, thereby avoiding the bony resistance of the forepelvis, the upper pubic arch, and the ischial spines. As it moves below the midpelvic plane, the vertex meets bony resistance at the sacrococcygeal platform, which causes it to move forward into the area of the inferior axis (Fig. 2—a, b, c). Rather than sweeping forward and anteriorly in accordance with the conventional description of the pelvic axis, the vertex continues downward in the direction as proposed by Caldwell. This is consonant with my personal belief that the vertex should be maintained in flexion and should not be allowed to extend during delivery until such time as the biparietal diameter of the vertex has passed through the bi-ischial diameter of the outlet, which means that the occiput has also by-passed the inferior border of the symphysis (Fig. 3). When extension occurs, the larger occipito-frontal rather than the suboccipito-bregmatic diameter of the foetal vertex passes through the inferior pelvic plane as when the head is well flexed. The extension that occurs during the course of second stage labour is at the expense of distension and often disruption of the structures within the perineum and the endopelvic fascia beneath the bladder. To prevent this the routine use of an episiotomy performed early as the vertex begins to crown is in keeping with modern obstetrics, with the objectives to avoid undue

pressure on the foetal vertex and damage to the mother's perineum and fascial supports of her bladder which otherwise might necessitate gynaecological surgery later.

Secondly, Caldwell placed considerable emphasis on the level and location in the pelvis at which the sacrum ends. In the normal pelvis the sacrum terminates at or below the level of the ischial tuberosities, and well posterior, as illustrated by an angle of 90° or more formed by a line drawn from the symphysis to the sacral promontory and from the latter to the tip of the sacrum. Briefly stated, the latter instance is consistent with a large sacro-sciatic notch and a divergent pelvic bore from inlet to outlet. An angle less than 90° means a convergent bore (Fig. 4) which may be readily offset in its implications by a sacrum which normally ends low in the pelvis. If, however, convergence is associated with a sacrum which ends high, that is, well above the ischial tuberosities, midpelvic and outlet contracture are likely to be encountered.

The height of the sacrum is best illustrated by constructing on the lateral film of Thoms method of X-ray pelvimetry lines representing the parallel planes of the pelvis located according to the concept of Moloy and Caldwell. In contrast to the planes of Hodge, these planes are drawn parallel to each other and at right angles to the coronal plane.

1st plane—at the level slightly below the superior strait;

2nd plane—at the level of the ischial spines;

3rd plane—at the level of the tip of the sacrum;

4th plane—at the level of the ischial tuberosities.

It will be seen that the distances between each plane may differ, sometimes considerably, depending on the depth of the pelvis and the level at which the sacrum ends. That is to say, in the normal pelvis the sacrum ends at or sometimes below the ischial tuberosities. Normally the 2nd and 3rd planes are a considerable distance from each other, while the 3rd and 4th planes may be near the same location. Actually, when the sacrum is long and ends very low in the pelvis, their respective locations can be reversed. These variations in location of the pelvic planes relate to the ease and difficulty of labour and delivery, especially in problems concerned with contracture of the midpelvis and/or the pelvic outlet. If the sacrum is long and ends low, even if it is set forward, the vertex will descend well on to the perineum, allowing it to take full advantage of the space available in the outlet (Fig. 5). By contrast, the vertex will fail to by-pass the sacro-coccygeal platform and descend to the perineum, if the 2nd and 3rd planes are in approximation, as when the sacrum ends well above the ischial tuberosities (Fig. 6). Here, to bring the vertex downward to the perineum by forceps may require marked traction, particularly if the sacrum is forward, with the possibility that severe trauma may result to the mother and the foetus. These findings are easily ascertainable on pelvic examination, and, together with the evaluation of the outlet, contracture of the lower pelvis is readily identified. It must be remembered that, when the sacrum ends at a high level, the posterior sagittal diameter of the outlet may be longer than normal, and in this circumstance the measurement is both erroneous and worthless.

Finally, opinion differs on how best to define and detect outlet contracture. It has been proposed by Moir (1951), Kaltreider (1954) and others that the antero-posterior diameter of the outlet (inferior strait), as measured from the lower border of the symphysis to the tip of the sacrum, is the most reliable index of the size of the outlet. It has been shown by Young and Ince (1940) that the length of this diameter of the outlet does not differ in the two sexes, but the same study revealed a marked difference in the area or usable space of the pelvic outlet in the male and the female pelvis, it being 78 sq. cm. and 93·7 sq. cm., respectively. Also, the average bi-ischial (intertuberous) diameter was 10·1 cm. in the female and 9·3 cm. in the male, while the subpubic angle was 93·5° in the female and 75·8° in the male. It is concluded that the adequacy of the outlet is determined by the flare of the arch and the length of the bi-ischial and posterior sagittal diameters as the latter related to the level of the sacral tip rather than by the length of the antero-posterior diameter of the inferior strait. Further, all of these estimations can be

FIG. 1

Superior and inferior axis in accordance with the concept of Caldwell *et al.*

FIG. 2a

Progressive normal descent of vertex in the superior axis in normal labour.

D.E.R.

FIG. 2b

Progressive normal descent of vertex in the superior axis in normal labour.

FIG. 2c

Progressive normal descent of vertex in the superior axis in normal labour.

FIG. 3

The vertex delivered in a state of flexion until the occiput is well beyond the symphysis. Median episiotomy preferred.

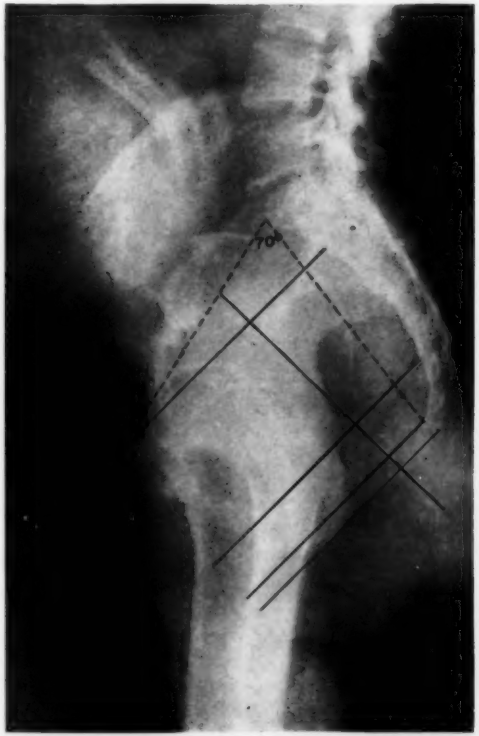

FIG. 4

Mrs. Pe.: A physician's wife. Android pelvis (77 per cent midpelvic capacity—Mengert). Convergent bore. Sacrum ends well above ischial tuberosities. Short first stage of labour; prolonged second stage. Firm low midforceps—infant 7 pounds. No sequelae. Future delivery: prognosis guarded.

FIG. 5

Mrs. K.: Small gynaecoid pelvis with android fore-pelvis (84 per cent midpelvic capacity—Mengert). Sacrum ends low. Easy low forceps—8 pounds 2 ounces infant.

FIG. 6

Mrs. Pa.: Small gynaecoid pelvis. Obstetrical conjugate 10·2 cm. (100 per cent midpelvic capacity—Mengert). Regarded as an inlet problem. *Sacrum ends high*. Roman type arch. Twenty-three hours labour with pitocin stimulation—"double set-up examination"—vertex +1–2 station—extraperitoneal Caesarean section—9 pounds infant.

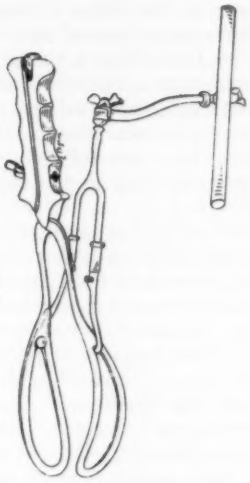

FIG. 7
The Irving forceps.

determined clinically, and X-ray examination of the outlet is unnecessary, despite the insistence of some.

The many facets of forceps operations are subject to individual opinion and reference will be made only to the instrument used. Besides the judgment and skill of the operator, a familiarity with one good instrument is an important ingredient in successful forceps operating. Rhodes (1958) has recently made a long-overdue suggestion that forceps be constructed according to measurements which may be considered safe for the mother and infant, for certainly forceps of bad design may apply unnecessary stress to the foetal head. It was gratifying to learn that the measurements recommended by Rhodes and presumably his peers at St. Thomas's Hospital as ideal were those of the instrument used in nearly all forceps deliveries in our clinic. In brief, this is a modified Simpson forceps with axis-traction appliance with special provision to keep the handle separated and thus avoid undue pressure on the foetal vertex (Fig. 7).

Regardless of the fact that the pelvis is thought to be normal on prenatal examination, we have found in our clinic that the method of delivery must on occasion be decided at a so-called "double set-up" examination. These are the few patients with borderline pelves or functional dystocia or both, in whom pelvic delivery is anticipated but who fail to make the progress expected in the latter hours of a trial labour. Careful assessment of the mid-pelvis and outlet and an estimation of the size of the foetal vertex by pelvic examination with the patient anaesthetized will afford the experienced clinician the necessary information for him to choose the correct procedure. The question to be answered is simply, what is the safest method of delivery for the mother and her infant? The choice is often between a mid-forceps procedure with or without the need for Dührssen's incision in the presence of borderline midpelvic or outlet contracture or Caesarean section on a patient who has usually experienced a long labour and may be potentially infected. This infrequent but extremely important group are those in whom the foetus is more likely to be damaged by ill-advised forceps delivery. In our institution the delivery is conducted in the operating room which has been made ready for either pelvic or abdominal delivery, and the anaesthesia is planned accordingly. When these preparations of "double set-up examination" are not made and the patient is managed in the case room, there is the tendency to deliver the patient pelvically, albeit unwisely. At least, this has been known to happen in our hospital and, I suspect, in most.

THE MANAGEMENT OF PROLONGED LABOUR

A labour exceeding 20 hours in duration, which in this discussion is the definition of prolonged labour, unquestionably is a major source of hypoxic damage in the foetus and newborn. It takes on special obstetric significance, for the infant is usually normal and mature in contradistinction to many other obstetric complications, such as late pregnancy bleeding where the foetus often suffers from prematurity with all its other hazards. At least 90 per cent of patients are in their first pregnancy, so that essentially it is a syndrome of primiparity. It has been amply demonstrated that prolonged

labour resulting from functional dystocia or a borderline cephalopelvic relationship with rare exception is followed by a normal labour and delivery. Consequently, pelvic delivery is sought whenever possible, especially in the younger patient, for assuming that the pelvis is normal or not appreciably contracted it affords the patient the assurance that she should experience little or no difficulty in future childbearing.

Because the aetiology of labour and the factors regulating myometrial contractility remain largely unknown, the treatment of prolonged labour remains largely empirical. Our management is predicated on the concept that the patient is afforded the usual supportive measures with periods of rest and attention to fluid balance, but that uterine inertia be treated energetically, not as a last resort measure but relatively early in the course of a prolonged labour. Although it could be debated whether uterine stimulants to shorten a desultory labour might be harmful, there is no doubt that if a high foetal morbidity and mortality rate is to be avoided, labour should not be permitted to exceed 30- to 40-hours duration.

In assessing the remote effects of labour, the writer wishes to recall that in his original study of prolonged labour he was struck by the fact that a few foetal deaths (3 per 1,000) occurred for no discernible cause in uncomplicated term labour and delivery. The autopsy findings were consistent with those found in intra-uterine asphyxia. It could be presumed that at least an equal number of the surviving infants might have suffered irreversible hypoxic damage. It was concluded that even normal labour contained an asphyxial element which becomes compounded in prolonged labour.

It is our practice to administer pituitrin in prolonged labour by the 18th hour, in the expectation that vaginal delivery will occur before the 40th hour. As this topic is due for discussion in a subsequent session, further details will not be given at this point.

In those cases where there is no appreciable progress with pituitrin therapy, a decision must be reached and preparations made to deliver the patient by the appropriate means. The method of delivery will depend basically upon the size of the pelvic outlet, the degree of cervical dilatation, the station of the presenting part, and the estimated size of the foetus. If the cervix is at least half dilated, the leading point of the presenting part is below the ischial spines, and the outlet ample, pelvic delivery is preferred with Dührssen's incision when needed. When these criteria are not fulfilled, abdominal hysterotomy is regarded as the safer method of delivery.

Finally, the place of medication for the purpose of pain relief in labour is one of the more controversial of the techniques used in the conduct of labour because of its possible adverse effect on the foetus by causing respiratory depression at birth. It is not the purpose of this discussion to become involved in the pros and cons of conducting labour in the technique of "psycho-prophylaxis" except to mention that the converts to this method have been led to believe by their reading and discussion that the use of medication during labour compromises the welfare of the baby leading to mental retardation and perhaps to cerebral palsy. This places the patient who accepts the implied tenets of psycho-prophylaxis in the position that, if she requests medication and anaesthesia, she at once demonstrates her inadequacy as a woman and compromises her child, both of which are repugnant to her.

Unquestionably, it is a matter of considerable consolation to the woman in labour to be assured that effective and safe methods of pain relief are available for her if the need arises. The control of pain is only one of the several advantages which medication affords. Safe and rapid induction of anaesthesia is easier in the medicated patient who requires operative delivery, and this facilitates either obstetric or surgical intervention which not only may be life-saving for the baby but will permit delivery without delay before it has been subjected to irreversible asphyxial damage. Although the development of extreme foetal distress from accidents in the course of normal labour is infrequent, these are the cases which may lead to irreversible damage to the central nervous system. This point is emphasized to impress the experimentalist, paediatrician, neurologist, psychiatrist, social scientist, and others who are interested in studying the remote effects of obstetrical

hazards on the individual. It is only the obstetrician who can appreciate the seriousness of the situation, where in the presence of a prolapse of the cord the baby could be born in a matter of minutes were the patient sufficiently medicated to accept an anaesthetic of sufficient depth to permit immediate operative delivery.

The summation of the experience of our current authorities in the field of obstetrical anaesthesia tends to support the view that the foetal mortality and morbidity is less with conduction anaesthesia in comparison with general anaesthesia. Account must be taken, however, of the obstetrical circumstances surrounding the cases analyzed. If the patients are individualized and no one form of anaesthesia is used routinely, it is often found that the less complicated cases are delivered under spinal or local block anaesthesia and the more complicated under the inhalation type. As Apgar (1957) has shown, although the foetal mortality and, presumably the morbidity, in Caesarean sections were higher under cyclopropane than spinal anaesthesia, cyclopropane was used in the emergency sections because of urgency of the procedure as well as for other reasons. This is an example of only one of the many variables encountered in the assessment of the possible foetal effects with the various forms of anaesthesia.

Excessive medication for pain relief given to the mother during labour is avoided by an awareness of the obstetrical problems and reasonable anticipation of the time of delivery so that medication is given according to the needs of the individual patient rather than "by the clock". Essential to optimal obstetric patient management is to provide anaesthesia comparable in quality to that provided for surgical patients in any good present-day hospital.

Conclusions

Despite the probability that the number of cases of mental retardation and congenital defects may temporarily increase because current medical care will allow more individuals so afflicted to survive, there is every reason to believe that these conditions, although not curable, may be preventable. When the normal span of foetal existence is prematurely interrupted, the meagre evidence suggests the probability that the *milieu* rather than the foetus *per se* is largely at fault. Further, infants born alive and surviving with such common and permanent handicaps as cerebral palsy are rarely the products of pregnancies which have been normal in all respects.

The avenues to be explored appear unlimited and must not be circumscribed, for here research addresses itself to all phases of growth, both normal and abnormal. It is only in this broad context that effective medical planning for generations yet unborn can be made. This is in keeping with Medicine's greatest successes which have come through the intelligent adjustment of Man's environment which has so greatly reduced the physical and infectious hazards once threatening humanity. Life in its beginning also has an environment which seemingly could be manipulated beneficially had we but the knowledge required for so doing. More properly, is not the ultimate aim of medical science to prevent disease? This effort must begin by protecting the new individual *in utero* and during the process of birth.

Thus, both the clinician and the biologist must respond to this challenge. The clinician must continue to direct his attention to developing policies of patient management and champion the acquisition of hospital facilities and medical personnel that will afford maximum protection to the mother and assure her that her infant will be born without handicap.

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PHYSICAL AND MENTAL HANDICAP IN THE PREMATURELY BORN

BY

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"I that am rudely stamped, deformed, unfinished, sent before my time into this breathing world scarce half made up, and that so lamely and unfashionable that dogs bark at me as I halt by them."
(Shakespeare. *Richard III*)

WHAT happens to prematures? In spite of the numerous studies carried out over the past 30 years, there is still no clear answer.

Capper (1928) wrote: "the immature infant becomes the backward school child, and is a potential psychoneurotic or neuropathic patient and even a candidate for the home for imbeciles and idiots", whereas Hess, Mohr and Bartelme (1934) considered that "premature birth unassociated with intracranial injury does not affect mental development".

Some of the confusion in assessing the effect of prematurity on later development is due to the rather unsatisfactory definition laid down by the World Health Organization in 1948: "An immature infant is a live born infant with a birth weight of 5½ pounds (2,500 grams) or less; if weight is not specified, a period of gestation of less than 37 weeks may be considered as the equivalent of prematurity." Approximately 7 per cent of all births in Great Britain are considered premature on this basis but, as shown in Figure 1, which is adapted from data given in the Ministry of Health Report for 1957, England and Wales, 45 per cent of these are over 4 pounds 15 ounces (2,250 grams) at birth. Owing to the increase in stillbirth and neonatal death rates as birth weight decreases, of those prematures surviving for longer than 28 days over 56 per cent are

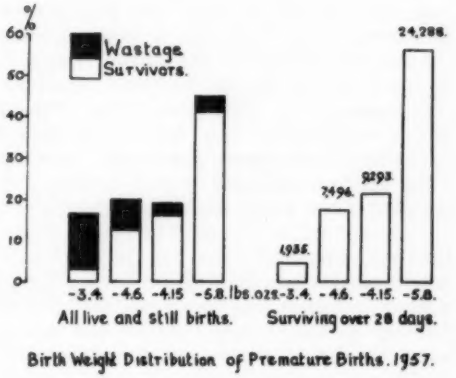

FIG. 1

Birth weight distribution of all births of 5½ pounds or less, England and Wales, 1957, showing wastage rates and numbers surviving for longer than 28 days in four birth-weight groups.

5 pounds or more at birth. A previous study of the aetiology of prematurity in Edinburgh (Drillien, 1957) showed that in between 37 and 49 per cent of births considered premature on a weight basis the recorded gestation time was 38 weeks or longer. These babies, nearly all over 4½ pounds at birth, were born in general to small mothers, often from a poor social background, and should not be considered premature. Studies such as the current National Survey (Royal College of Obstetricians, 1948), which includes all children of 5½ pounds or less at birth born in England and Wales in one week

in 1946, are so heavily overloaded by these small but full-time children that the real effect of premature birth on later development may well be overlooked.

The data to be presented here are based on two groups of children:

Group I consists of 92 children, born between 1948 and 1959, whose weight at birth was 3 pounds or less, and Group II consists of 600 children, born between 1953 and 1955, approximately two-thirds being 5½ pounds or less at birth, and one-third mature controls. Of the prematurely born about one half were 4½ pounds or less at birth. These children have been seen at regular intervals since birth in their own homes. Over 90 per cent of those originally enrolled still remain in the survey. Those in Group I born in the last five years have been seen regularly, and those born before 1953 on one or two occasions only. All children studied in retrospect were traced, and all but one of the living children examined. Seven children (7·6 per cent) in this group died after discharge from hospital and before the age of two years, 5 have been lost by removal before this age, and 9 have not yet reached two years. The following figures refer to 71 children who have passed their second birthday. By this age major physical and mental handicaps should be apparent. Results of later intelligence testing in school show a close correlation with assessment at two years, especially at the lower I.Q. levels. The real age of the child (i.e., chronological age minus weeks of prematurity) has been used in calculating acceleration or retardation in growth and mental development.

Group I

Physical Growth

Figure 2 shows the weights of 70 children at the time of their last examination, expressed as acceleration or retardation of weight-age, weight-age being the age at which a normal child would have the weight of the child in question. Figures for normal weight and height have been taken from means for Edinburgh pre-school and school children 1951–1956 (Ellis, 1956). Only 11 per cent of the group were up to or above the expected weight for their age, and 10 per cent were the weight of children half their age. Figures for height are similar, though the retardation in height is not so marked, the majority being underweight for their height, as well as small for their age. There is no apparent tendency for physique to improve with age, the proportion of undersized children remaining steady throughout the age period two–nine years.

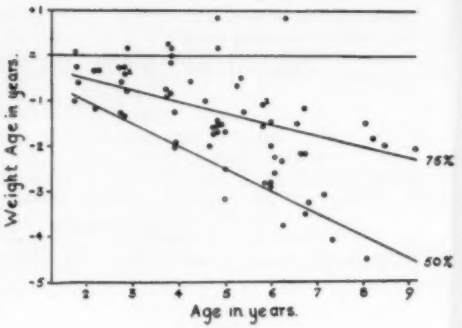

FIG. 2

Acceleration and retardation in weight-age of 70 children, aged two to ten years, who were 3 pounds or less at birth.

Mental Development

Small stature by itself is not necessarily a handicap, as long as the child is healthy and of good intelligence.

Figure 3 shows the estimated intelligence of 71 children, 42 of whom have reached the statutory age for school entrance. The most recent assessments of these 42 children have been carried out mainly by the school Child Guidance Department. Black circles represent children who are unable to attend normal school because of physical disability, and include cases of cerebral palsy and defective hearing and vision. Crosses indicate children with a physical handicap which, though likely to affect school progress, does not necessarily preclude the child from normal schooling, and includes milder cases of cerebral palsy, epilepsy, and less serious defects of vision. Twenty-two per cent of the group have a major physical handicap.

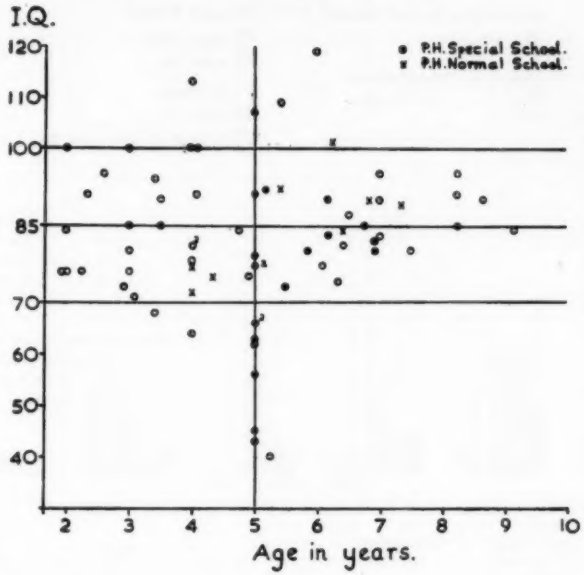

FIG. 3

Intelligence quotients of 71 children, aged two to ten years, who were 3 pounds or less at birth.

Fourteen per cent of the total have an I.Q. of less than 70, and will not be educable in normal school (the level for special schooling for mentally handicapped being 70–75). Forty-nine per cent, with an I.Q. between 70 and 85, are dull, and will probably need special educational treatment in adjustment classes within the ordinary school, although the presence of added physical handicap, or abnormality of behaviour (which is common in this low birth-weight group) may result in transference to special school. Only 9 children (13 per cent) are considered to be of average or above average intelligence. A minimum of 27 per cent of the group will require special schooling because of mental or physical handicap or both.

GROUP II

It is well known that prematurely born children tend to come from a poor social background. In the larger survey group it is obvious that mothers of the mature controls tend to be of better intelligence as well as being more prosperous than mothers of the prematurely born. One would expect on these grounds alone that the prematures would themselves be less intelligent than their full-term contemporaries. All these children are now between four and six years old. Figure 4 shows the proportion of children in four premature birth weight groups who already need or who are expected to need different types of schooling, as compared with children matched for sex, family placing, and social background, but mature at birth. No difference was found between those prematures over 4½ pounds and matures from a like background, though both groups had a lower mean I.Q. than that of the total mature sample, as would be expected, since they tend to come from a poorer background. Children with an I.Q. below 55 will ultimately need some type of

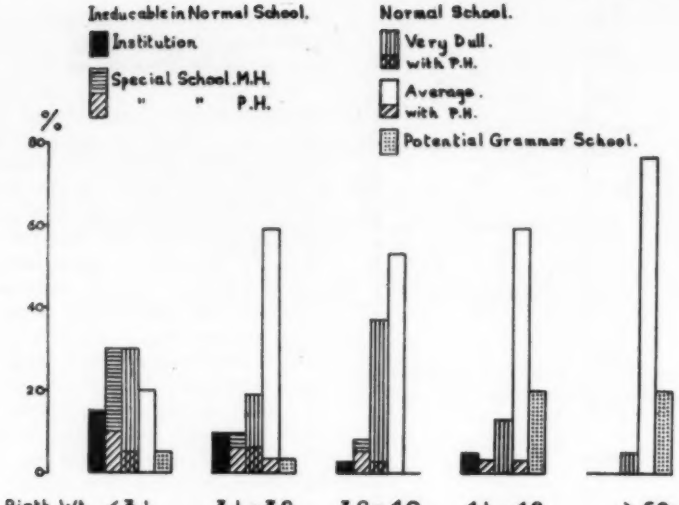

FIG. 4

Type of schooling required for prematurely born children of different birth weight, compared with matched maturely-born controls.

institutional care. Children with an I.Q. level above 110 are potential candidates for Grammar School.

The percentage of children requiring special schooling for all types of handicap increases strikingly with decreasing birth weight, being 29 for those smallest at birth, 10 for those between 3½ and 4½ pounds, and 3 for the total school population in Scotland (Scottish Education Department, 1958). The percentage of children requiring special schooling for mental handicap is 21·1 for those 3½ pounds or less at birth, and 6·9 for those between 3½ and 4½ pounds, compared with a figure of 1·9 for the total school population in Scotland. If it can be assumed that the prematurely born children in this survey are representative of prematures in the general population, it seems likely that premature birth accounts for a minimum of one in eight of all mentally handicapped children.

Sixty-four children in the main survey have entered school and have been given the Terman and Merrill L test in their second or third term. Mean I.Q. for those of 4½ pounds or less at birth was 92, compared with 103 for those between 4½ and 5½ pounds, and 108 for mature controls. These means are based on small numbers, but show a similar trend to pre-school findings. The survey indicates that while mental retardation and physical handicaps are much more common amongst prematurely born children, the incidence increasing with decreasing birth-weight, nevertheless, amongst prematurely born children of like birth-weight there is a considerable variation in the level of intelligence and degree of handicap. For instance, one boy with a birth-weight of 2 pounds 15 ounces has an estimated I.Q. at seven years of 119.

In Group II, 46 children were considered to be mentally or physically handicapped at two years, and these have been matched with children

TABLE I

	Handicapped Children	Not Handicapped Matched for Birth-Weight	Mature Controls
	Percentage		
1. Age of mother:			
(*a*) 30 years and over	50	37	36
(*b*) 35 years and over	15	13	2
2. Complications of pregnancy:			
(*a*) Chronic illness of mother	15	3	2
(*b*) No complications	48	45	90
3. Maternal grade:			
(*a*) Middle class and superior working class	11	50	58
(*b*) Average working class	46	39	36
(*c*) Poor working class	43	11	6

TABLE II

Reproductive History

Conceptions Resulting in Abortion, Stillbirth, Neonatal Death, or Live Born Child 4½ Pounds or Less	Handicapped Children	Not Handicapped Matched for Birth-Weight	Mature Controls
	Percentage		
All previous conceptions	52	31	19
All subsequent conceptions	31	13	2
Conception immediately before or after	29	17	7
Relative infertility	37	14	10

of like birth-weight, age, and sex, but with no apparent handicap, and also with an equal number of mature controls. These three groups have been compared for age of mother, social background, complications of pregnancy, and previous and subsequent obstetrical history of the mother. The findings are shown in Tables I and II. It is likely that in the mature control group there will be an excess of older mothers and mothers with a previously unfavourable obstetric history, as compared with the general population, as these cases will be given priority in hospital booking.

There is a higher percentage of older mothers in the handicapped group, which would be expected, as the incidence of both congenital abnormality and premature birth rises with age.

The incidence of complications of pregnancy in the two matched groups is approximately equal except for a higher incidence of chronic illness of the mother in the handicapped group, but the numbers are small and not statistically significant. The most striking difference in Table I is seen in the proportions of mothers graded as poor working class, there being 4 times as many in the handicapped group as compared with the matched controls and 7 times as many as compared with the mature controls. Most of these women appear to be of low intelligence themselves, the fathers are employed, often sporadically, on unskilled work, and standards of household management and child care are low.

A similar association between maternal grade and early development became apparent when

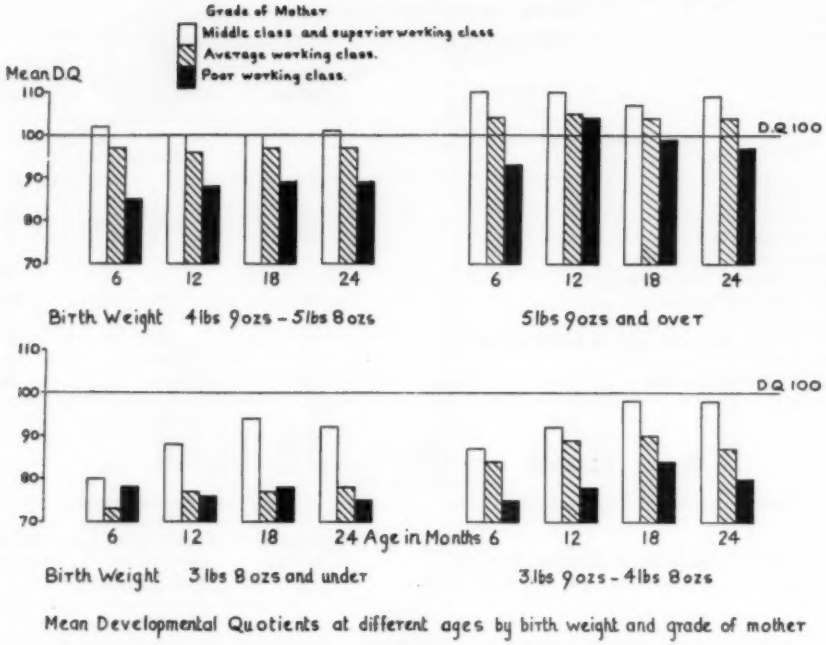

FIG. 5

Mean developmental quotient at ages six months to two years, by birth weight and maternal grade.

studying mental development in the first two years of life, using Gesell developmental tests. Figure 5 shows mean developmental quotients (which are roughly equivalent to I.Q.) in children of like birth-weight born to mothers graded as being middle class or superior working class, average working class, and poor working class. For all maternal grades, mean D.Q. at two years rises steadily with increasing birth-weight. In the smaller premature groups (i.e., those 4½ pounds or less at birth) there is an improvement in developmental ability in children born to the best type mothers, but not in those from average and poor homes. Those who were over 4½ pounds at birth show little variation in mean D.Q. at different ages in any maternal grade, except in the mature control group where children from the worst homes score higher at one year than at two years, this being due to backwardness in speech. The difference in D.Q. at two years in children from the best and worst homes is much more marked in the smaller prematures than it is in those over 4½ pounds. It seems likely that a combination of inferior genetic endowment and a poor environment has a more marked effect on early development in those who were also premature than it does on maturely born children from a similar background.

The incidence of immediate postnatal symptoms which might suggest birth-injury, such as delay in establishing respiration, shock, cyanotic or apnoeic attacks, cerebral crying, irritability and twitching, increases markedly as birth weight decreases from 6·2 per cent in the mature control group to 28·6 per cent in those

3½ pounds or less. However, in this sample there was no apparent difference in later development between children of like birth-weight who did or did not exhibit such symptoms.

It is probable that premature babies are more likely to sustain cerebral damage as a result of birth injury, and that in some cases mental retardation and cerebral palsy may result, but it also seems likely that in more cases postnatal symptoms which are commonly attributed to cerebral damage are, in fact, due directly to the immaturity of the baby.

When the previous and subsequent obstetric history of the mothers was considered, quite definite differences were found, as shown in Table II. For mothers of the handicapped group, 52 per cent of all previous conceptions and 31 per cent of subsequent conceptions resulted in an abortion, stillbirth, neonatal death, or a live born child 4½ pounds or less at birth, the comparable figures for the matched group being 31 and 13, and for the mature controls 19 and 2.

Similarly, in the handicapped group it was much more likely that the conception immediately preceding or following the affected child also resulted in an abnormal outcome. The incidence of relative infertility (i.e., where the mother has had difficulty in conceiving or producing a live born child) is very much higher for those who subsequently produce a handicapped child. Thirty seven per cent of mothers in this group give such a history. Forty-four conceptions, of which 19 were lost by abortion, stillbirth, or neonatal death, were recorded for 163 years of marriage, i.e., one live born child for every 6½ years of marriage. Contraception following the birth of an abnormal child did not appear to be a major factor in restricting family size.

Three cases in which the mother was considered infertile are of special interest, as they suggest that the fault may sometimes be with the father rather than with the mother:

Case 1. Mother, aged 17, had an illegitimate baby, weighing 5 pounds 8 ounces in 1939. She married in 1948 and had three abortions before producing in 1953 a 4 pounds 11 ounces girl with a cleft palate. The parents are anxious to have another child, but the wife has not conceived in the last six years.

Case 2. Mother, aged 19, had an illegitimate child weighing 7 pounds in 1952. She subsequently married in 1955, and in the last four years has produced a live born female (4 pounds 4 ounces), a stillborn male (2 pounds 14 ounces), a female who died shortly after birth (3 pounds 2 ounces), and a live born female weighing 2 pounds 2 ounces.

Case 3. Mother had three normal full-time children by her first husband. After his death she re-married, and subsequently had four abortions, followed by a 2 pounds 9 ounces male, who is a case of mixed cerebral palsy.

A similar increase in relative infertility was found by Ingram (1955) who studied the reproductive history of mothers of 79 congenital diplegic children born in Edinburgh between 1938 and 1952. The mothers of diplegic children had fewer pregnancies, which were more widely spaced, prior to the birth of the affected child, as compared with the mothers of children with acquired hemiplegia associated with birth injury. They also had a higher incidence of abortion and stillbirths.

It is hoped during the next three years to pursue this line of investigation further, and review children born to mothers who have attended an infertility clinic, or who have a history of recurring abortion and stillbirth. It may be possible to define more closely those women who have a high risk of producing an abnormal baby. From the practical point of view, this is important, as it would raise the question whether medical attempts to combat infertility are always desirable.

Summary

A study of the later development of: Group I, 92 children, born between 1948 and 1959, who were 3 pounds or less at birth, and Group II, 600 children of all birth-weights, born between 1953 and 1955, led to the following conclusions:

Group I

Physical Growth. The majority of the children were considerably retarded in weight and to a lesser extent in height. Only 11 per cent were at or above the expected weight for their age.

Mental Development. Fourteen per cent of the total had an estimated I.Q. less than 70 and will need special schooling; 49 per cent with an I.Q. between 70 and 85 were considered very dull.

Only 13 per cent were considered average or above average in intelligence.

Physical Handicaps. Twenty-two per cent of the total have a major physical handicap.

Group II

Prematurely-born children were found to come from a poorer socio-economic background than the mature controls. When the prematures were matched for sex, family placing, and social background with children mature at birth, it was found that there was no difference in subsequent mental development between those prematures who were over 4½ pounds at birth and the control group. Children with a birth weight of 4½ pounds or less showed an increasing proportion of dull, retarded, and grossly defective cases as birth weight decreased.

When the mothers of handicapped children were compared with those of infants of like birth weight but without handicap, and those of mature controls, the following factors appeared to be of importance in the handicapped group:

(1) An excess of older mothers.

(2) A striking increase in the incidence of poor working class mothers.

(3) A higher incidence of previous and subsequent abnormal pregnancies, and a higher incidence of relative infertility.

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PREMATURITY AND DEVELOPMENT

BY

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IN order to demonstrate whether an increased risk of developing neuropsychiatric disabilities is associated with an abnormal condition, the more time-consuming longitudinal investigations are necessary. Cases with the condition to be studied, preferably one likely to be productive of damage, and suitable controls are selected at birth and followed with serial examinations. Such a study of prematurity has been conducted in Baltimore, Maryland, since 1952 (Knobloch *et al.*, 1956). In addition to demonstrating causal relationships, this study has also refined the criteria for the early identification in infancy of those children likely to develop a variety of neuropsychiatric problems later in life.

Only a brief outline of the study can be given at this time. Single-born premature infants and full-term controls matched for race, parity, hospital of birth and socio-economic status were selected. At 40 weeks of age a history was obtained and a Gesell Developmental and Neurologic Examination and a physical examination done. In the case of the premature infants, the chronological age was corrected for the estimated amount of prematurity and the examiner did not know at the time of the evaluation whether the infant was premature or a control. Eighty-five per cent of those originally scheduled for examination were actually seen; 3·5 per cent refused and the remainder could not be located.

One of the major findings of the study is that, as the birth-weight of the infant decreases, the amount of disability in a variety of aspects of growth and development increases. In regard to neurological status, for example, 26·3 per cent of those infants with a birth-weight of 1,500 grams or less have neurological abnormalities of sufficient degree to cause serious concern about their future development. The comparable figures for the remainder of the premature infants and for the full-term controls are 8·2 per cent and 1·6 per cent, respectively. Corresponding figures for the percentages of those with minimal cerebral damage, which we believe to be the precursor of later learning and behavioural difficulties, are 22·8 per cent, 16·0 per cent and 10·0 per cent, respectively. Again, 17·6 per cent of the smallest prematures have defective intellectual functioning, the comparable figures for the remainder of the prematures being 1·8 per cent and for the full-term control infants 1·6 per cent. At a comparable age premature infants, on the whole, are one half to one inch shorter and five hundred to one thousand grams lighter, have two to three times as many physical defects, and have 50 per cent more illnesses than full-term control infants (Knobloch, Pasamanick *et al.*, 1959). When the presence of serious neurological abnormality resulting from cerebral damage is taken into account, the physical disadvantage of the premature infants is even more marked.

Prematurity generally has a deleterious effect and fully 50 per cent of those infants weighing fifteen hundred grams or less at birth have handicaps ranging from minimal neurological damage to severe mental deficiency with blindness. There is a history of abnormal behaviour pattern, such as twitchings, convulsions, changes in muscle tone, and sucking and feeding difficulties, which increase as the amount of neurological abnormality increases, and similarly the percentage of mothers called tense and uncertain goes up as the neurological abnormality is more severe (Knobloch and Pasamanick, 1959b).

There is an increase in the percentage of babies with low birth-weights (Rider, Taback and Knobloch, 1955) and an increase in the complications of pregnancy (Knobloch, Pasamanick and Lilienfeld, 1956) in those groups which are socially disadvantaged, but in the first year of life, when a probability sample of infants is studied, no differences in behavioural functioning can be demonstrated on the basis of race, education of the parents or socio-economic status. When the developmental quotients for the entire groups are adjusted for the race and birth-weight distributions to be expected in a surviving population, only 1·5 per cent of the infants have developmental quotients below 80 (Knobloch and Pasamanick, 1959a). Exogenous organic factors, both neurological and physical, can be demonstrated in almost all of them. In addition, three-fourths of these infants are premature with more than 50 per cent having a birth-weight of less than 1,500 grams, compared to a 5 per cent representation of this birth-weight group in the entire premature sample, and with a high incidence of the chronic anoxic complications of bleeding and toxaemia.

At 40 weeks of age the question of whether there is an increased risk of abnormality associated with prematurity can be answered in the affirmative. But this is of only academic interest unless the infant examination has predictive value for the future. Although previous studies have decried the usefulness of infant "testing" and have reported correlations ranging from 0·2 down to small negative ones, the correlation between our findings at 40 weeks and at 3 years of age is 0·5 for the entire group and 0·75 for infants with neurological or intellectual abnormality. Fifty per cent of these infants change less than 10 points and 75 per cent less than 15 points in their developmental quotients in this period of time.

At three years of age the differences between premature and control infants are still present, but there is a sharp divergence between the white and Negro children. In contrast to comparable developmental quotients in all fields of behaviour in the control infants at 40 weeks, by three years of age there is a marked dichotomy in those areas of behaviour where socio-cultural influences exert their greatest effect. Adaptive behaviour rises to 111 and language behaviour to 106 in the white children while the comparable quotients fall to 97 and 90, respectively, in the Negro group. However, no differences in either gross or fine motor behaviour are observed between the two racial groups. In infancy, therefore, the socio-cultural level of integration appears to act on the psychological level only by way of the biological level of integration through increased damage. In later childhood, however, the more direct effect on psychological functioning of socio-cultural differences becomes apparent.

While the amount of abnormality we have found in these smaller babies is high, it is lower than that reported by Drillien (1959) in a group of comparable birth-weight. The difference may possibly be explained by the fact that only single births were included in our sample, since morbidity as well as mortality rates are much higher in multiple pregnancies.

The findings of the retrospective and anterospective studies mutually reinforce each other. They indicate that there is a relationship between the complications of pregnancy and the development of physical as well as neuropsychiatric disabilities. They also indicate that the increase in neuropsychiatric disabilities in the low socio-economic groups can be accounted for in large measure by an increase in cerebral damage consequent to a higher rate of the complications of the prenatal and paranatal periods.

Obviously, not all possible aetiological factors have been investigated so far, and no results of our current anterospective studies of bleeding and toxaemia, similar to the one of prematurity,

are available at the present time. All of the findings to date, however, suggest that there are practical, medical, social, and educational measures that can be directed towards eliminating those factors already known to be aetiological and thus reducing the burden of neuropsychiatric disorder.

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AETIOLOGICAL FACTORS IN PREMATURE LABOUR

BY

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MY contribution to this symposium deals with the immediate problem of premature labour as an obstetrical hazard affecting actual survival rates rather than with the subsequent progress of the premature infant. Moreover I do not intend to deal at all with techniques for the delivery or immediate after-care of such infants, but rather to study the basic problem, which is surely our lack of any real knowledge of the causes of spontaneous premature labour. It may, perhaps, be considered as a digression from the main theme, but the deviation is deliberate.

The extent of the problem is well known; figures from different sources vary only slightly, and prematurity and its complications are seldom responsible for less than 50 per cent of neonatal deaths. This may at first sight seem essentially a problem for the paediatrician, but it is doubtful whether further refinements in nursing and therapeutic techniques will make any substantial impact on the overall picture. It is more probable that any marked change would come about only as we, as obstetricians, gain a fuller understanding of the supposed causes of spontaneous premature labour (and perhaps even find some way of arresting it), and find further alternatives to the induction of premature labour in the management of certain complications of pregnancy.

It was with this object in mind that I studied the records of some 1,186 instances of premature labour (concerning whom adequate data were available) occurring at the Brisbane Women's Hospital during a recent four-year period. Both public and private, booked and unbooked, cases are included. The usual criteria of prematurity apply to this series (Table I).

The proportion of prematurely born infants remained very constant during the period under review, with an average of 5 per cent of all live born infants delivered during that period. The nutritional and general economic status of the mothers of these infants was, for the most part, entirely satisfactory. Infant mortality from prematurity varied little from year to year, with

TABLE I

Incidence of and Mortality from Prematurity, Brisbane Women's Hospital, 1950–53 Inclusive

Year	Live Births	Live Born Premature Births	Incidence Per cent	Deaths of Premature Infants	Infant Mortality Per cent
1950	8,586	396	4·6	38	9·6
1951	9,199	512	5·5	56	10·9
1952	9,871	505	5·1	55	10·9
1953	9,971	501	5·0	51	10·2
		Average ..	5·0		10·4

TABLE II

Supposed Main Aetiological Factor	Number of Cases	Incidence Per cent	
No known cause	320	27·0	
Premature rupture of membranes	146	12·3	43·0
Habitual premature labour	45	3·7	
Pre-eclampsia	264	22·3	
Eclampsia	15	1·3	
Essential hypertension	47	3·9	
Chronic nephritis	7	0·6	52·5
Multiple pregnancy	146	12·3	
Placenta praevia	52	4·4	
Accidental and unexplained haemorrhage	91	7·7	
Miscellaneous causes	53	4·5	
Total	1,186	100·0	

an average loss of 10·4 per cent. Throughout this period a highly experienced person was in charge of the premature infants' nursery.

Of the 1,186 instances of premature labour selected for study, the onset was spontaneous in 851 and induced in 335. Table II is an attempt to tabulate the main aetiological factors which had apparently precipitated or necessitated the premature onset of labour in each instance. In general terms it will be noted that in 43 per cent no known cause could be ascribed, in spite of adequate data in other respects. This is a typical finding in comparable series, and represents the hard core of the problem. Of the remaining 57 per cent in which a definite cause could be ascribed, the three major categories of pregnancy toxaemia, ante-partum haemorrhage, and multiple pregnancy, comprise 52·5 per cent.

Having made a survey of this kind it is always interesting to compare the findings with similar observations carried out elsewhere, and this I have done, using data from Aberdeen (Baird, 1945), London (Nixon, 1953), Dublin (Feeney, 1952), and New York (Pomerance and Steiner, 1950; Bookstaver, 1951). This is not the time to make detailed comparisons, but certain general trends are clear, thus the "cause unknown" group consistently comprises between 40 per cent and 50 per cent of the total. The incidence of premature labour resulting from pregnancy toxaemia varies widely for reasons which cannot be considered here. The proportion of premature births resulting from placenta praevia appears to be extremely constant, with an average of 3·6 per cent but the incidence of premature labour from accidental haemorrhage cannot properly be appraised because of the inclusion in some series of the unexplained as well as the truly retroplacental antepartum haemorrhage in this category. The incidence of premature labour primarily due to multiple pregnancy is also remarkably constant, with an average of 13·8 per cent and a range of only 12·3 per cent to 17 per cent in the different series.

As I have remarked, the core of the problem relating to foetal hazards through prematurity lies in the substantial proportion of completely unexplained and often repeated premature births. We know very little about this category, but obstetrical enquiry over the last decade has followed three main trends; first, are there deficiencies in the endocrine balance or in the uterus, cervix or foetal membranes not immediately obvious on examination, and if so what can be done about such deficiencies?; secondly, are sociological factors and dietary deficiencies responsible, and if so exactly how do such factors operate, and what precise deficiencies are concerned?; and thirdly, are psychogenic factors responsible?

In regard to possible deficiencies in the cervix, uterus, and membranes, the concept of undue fragility of the foetal membranes has been put

forward on a number of occasions but is difficult to prove or disprove, and in the present state of our knowledge is not amenable to treatment.

Incompetence of the internal cervical os as a cause of repeated, apparently unexplained, late miscarriages and early premature births, even in primiparae, is now established as a clear-cut clinical entity. The condition may be congenital, or may have been preceded by surgical dilatation of the cervix for dysmenorrhoea prior to marriage, in which case it may co-exist with an "irritable" pregnant uterus and raised intra-uterine tension. Treatment by a well-timed and well-placed cervical suture, together with therapy to reduce uterine irritability appears to offer slightly increased chances of obtaining a viable infant in some of these patients.

It is my impression that previously infertile patients known to have a hypoplastic uterus, and who conceive with difficulty, are more at risk in regard to miscarriage and premature labour than other cases of primary infertility. Is this simply a further manifestation of their general hypogonadal status? Could it be that there is inadequate growth response of the myometrium with increasing intra-uterine tension? I believe that this is occasionally so, and I treat such patients appropriately.

Other presumed or evident manifestations of endocrine imbalance have not in the past pointed the way to any really satisfactory prophylactic regime. A new ovarian derivative, a water-soluble non-steroid hormone extracted from the corpora lutea of pregnant sows, has been subjected to therapeutic trials with varying degrees of success. It appears to be more promising in the very early stages of threatened premature labour. Our own limited experience with this agent has not been encouraging, but it would seem worthy of consideration and further clinical observation.

In the endocrine field I would make one further speculation in passing. As Hawker (1956) and others have shown, there is, during normal pregnancy, a thousand-fold increase in the concentration of a plasma enzyme that destroys the posterior pituitary hormone. This enzyme is equally effective against the oxytocic as against the anti-diuretic fraction. It has been postulated (Page, 1957) with substantial evidence that a proper balance between production and destruction of the anti-diuretic fraction is essential for proper water and salt balance during pregnancy, viz., for the prevention of toxaemia. Could it be that, by the same token, a proper balance between the production and destruction of the oxytocic fraction is essential for the prevention of at least some instances of spontaneous premature labour? The technique of intravenous oxytocin infusion has shown us that the establishment of premature uterine contractions by this means is largely determined on a quantitative basis.

We know so little about these destroying plasma enzymes that this postulate does not at the moment open the way to any form of treatment. However, there is another thought in this connexion; now that an effective oxytocic agent has been synthesized, could this not lead to the synthesis of an anti-oxytocic substance which would arrest premature uterine contractions?

Nutritional deficiencies *per se* as a cause of spontaneous premature labour can no longer be regarded as truly valid. Methods used to assess the state of nutrition in human beings are notoriously unsatisfactory, and even under conditions where the national dietary level was grossly reduced as in post-war Holland and Germany, there was, in spite of a tendency to smaller babies, no consistent evidence of an increased tendency to premature labour. In North America neither Williams and Fralin (1942) nor Dieckmann (1945) could find any correlation between specific vitamin, mineral, and protein deficiencies, and premature labour.

As to unfavourable housing and living conditions as a significant factor in the incidence of spontaneous premature labour, there is a good deal of published evidence that would suggest that this is so, and yet there are countries such as Australia where the standard of living (with a few obvious exceptions) really varies very little and yet the incidence of unexplained premature labour remains constant at a figure little less than that generally quoted.

In the United Kingdom, too, a carefully controlled study of some 13,257 recently-confined patients from every walk of life, carried out by Douglas (1950) indicated a low incidence of premature labour in the particularly

prosperous 9 per cent of the community, but found no evidence of social, economic, or nutritional factors in the remaining 91 per cent.

I submit that it is amongst this 91 per cent rather than amongst the poorly housed and poorly fed, that we should seek for the causes of spontaneous premature labour, and in this connexion I pose my final question: to what extent, if any, are psychogenic factors responsible?

We know that gentle rhythmic contractions of the uterus are normally present from the twenty-first week of pregnancy. What would cause these gentle contractions to develop sufficient strength and intensity to provoke the membranes to rupture and subsequently to expel the foetus at varying periods of gestation? Although an increased production of adrenalin, under conditions of emotional stress, has long been recognized, the actual effect of adrenalin on uterine muscle contractility has been controversial since Rucker (1926) claimed that it had a relaxing effect, its use in the treatment of contraction ring being subsequently recommended. However, neither clinicians nor experimental physiologists have confirmed these observations. Kaiser and Harris (1950) studied the action of the two fractions of adrenalin extract separately and found that noradrenalin increased uterine contractility and that the remaining fraction decreased it. When using the whole extract it was noted that small amounts of adrenalin appeared to inhibit uterine action but that larger amounts had an oxytocic effect.

Alvarez (1953) produced evidence suggesting that, at least at the twenty-eighth week of pregnancy, uterine contractions are augmented by the intravenous infusion of adrenalin in high dilution. More recently, *in vitro* studies on the motility of the human uterus carried out by Sandberg and others (1958) in Stockholm demonstrated that the increased sensitivity to noradrenalin of the non-pregnant uterus during the secretory phase was still more pronounced in the pregnant uterus, especially in the lower segment.

Because so many unexplained premature labours commence with, or are preceded by, spontaneous rupture of the membranes (and I refer specifically to my own series), could it be that such rupture is an expression of increased intra-amniotic tension due in turn to uterine hypertonus, especially in the lower uterine segment?

It is my own belief that for the bulk of the community, reasonably well housed and fed, a study of psychogenic factors in the production of spontaneous premature labour would be most rewarding. The more common types of stress in this connexion are probably: (*i*) difficult and faulty personal relationships especially when frequent contact is unavoidable; (*ii*) the inevitable frustration of perfectionist types, especially with their second pregnancy; (*iii*) duties and responsibilities for expectant mothers out of proportion to their capabilities; (*iv*) behaviour problems with children of earlier pregnancies; and, by no means least, (*v*) the type of emotional immaturity which finds expression in frequent rages and tantrums.

If we really want to reduce the number of "unexplained" premature births we must tackle this problem by providing adequate opportunities for pre-marital instruction and post-marital counselling. Pregnancy should, as far as possible, be wanted. Patients should be encouraged to "talk out" their tensions at antenatal consultations. Child guidance clinics should be especially available to the expectant mother with behaviour problems on her hands. The short-term use of tranquillizers may occasionally avert a premature labour, and training in relaxation techniques can only be beneficial in this view. In actual fact we know, of course, that the solution goes much farther back—to the early childhood training and environment of the mother. Fortunately most mature, well adjusted, women can cope successfully with day to day tensions. However, in maladjusted emotionally immature women, such tensions may, because of the effect of noradrenalin on uterine activity, accentuate normal tonus even to the extent of precipitating spontaneous rupture of the foetal membranes; to be followed within a day or two by yet another "unexplained" premature labour.

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DISCUSSION ON THE HAZARD OF PREMATURITY

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THE TREATMENT OF CERVICAL INCOMPETENCE

I SHOULD like to dwell for a few moments on one aspect of the prophylaxis of prematurity, namely, the treatment of cervical incompetence, and I should like to present the results in 10 cases. From the literature the following list of aetiological factors has been compiled: (1) hormonal imbalance, (2) congenital defects of the internal os, (3) spina bifida occulta, (4) previous dilatation and curettage, (5) previous abortion, (6) vaginal hysterotomy, (7) precipitate labour, (8) difficult forceps, and (9) repair operation. Of them all, the fourth and the ninth are the two to which I draw your attention as I feel that these operations are particularly likely to be followed by this condition.

As regards treatment, Shirodkar in 1953 first described a surgical procedure carried out during pregnancy and designed to keep the cervix closed. This consisted of placing around the cervix a suture of fascia lata or of ¼-inch nylon tape by means of specially designed needles and tying the suture tightly in front. Subsequently at term elective Caesarean section was required. Since 1957, following a paper read at the Ulster Obstetrical Society by Gibson, we have been using a simpler technique at the Royal Maternity Hospital, Belfast, consisting of placing two purse string sutures of wire round the cervix. Silver and tantalum have been used, but at present stainless steel wire, S.W.G.34, is the material of choice. Patients are selected on their history alone. No attempts have been made to carry out X-ray methods of diagnosis. After the twelfth week, the patient is anaesthetized and the cervix exposed using a duck bill speculum and two lateral vaginal retractors; adequate exposure is very important and an assistant is required. A piece of stainless steel wire is threaded on a cutting needle and the cervix is pulled down with a sponge forceps; deep bites are taken at the junction of the cervix and vaginal vault at 3, 12, 9 and 6 o'clock. The ends of the wire are then twisted in a clockwise direction (that is rather important when it comes to taking it out) until the cervix is closed without tension. The wire should not be too tight and it should be possible to pass the end of a Spencer Wells forceps through the loop of wire after it has been twisted. A second purse string suture is passed round the cervix about ½ inch nearer to the external os and again the wire is twisted. The two wires are knotted together and then cut flush to prevent the sharp ends doing any damage to the vaginal wall. After 24 hours the patient is allowed to go home; she is instructed to report back should there be any abdominal pain, bleeding or discharge. Coitus is not prohibited nor is any adjunctive therapy prescribed. At the 36th week the sutures are removed, usually without an anaesthetic. The knot is cut off and the wires are untwisted in an anti-clockwise direction and pulled out; occasionally the wire becomes embedded in rather a thickened hypertrophied cervix. Very often the cervix dilates up to 3 or 4 fingers and the patient goes into labour at once, but occasionally she is allowed to go home to await labour at term. In our 9 cases there have been 10 successful pregnancies as one patient has come twice.

One patient developed dysuria, possibly due to the fact that the wire was passing close to the bladder. The pregnancy went on quite well in spite of this dysuria and she was delivered of a live baby at term. Several patients were found to have the wire knot embedded in the posterior vaginal wall. It was very easily removed and caused no complications. The wire never came into the rectum. One patient was admitted to have the wires removed the following morning; she went into labour that evening but the night staff were not impressed until the head came

on to the perineum, whereupon they delivered a live baby. We had subsequently to take out the wires from a very badly lacerated cervix.

It is my belief that the diagnosis and treatment of the incompetent cervix is the greatest advance in obstetrics in the last 10 years. Suitable cases occur infrequently but if treatment were undertaken throughout the country the foetal salvage must be considerable. As I said, it is not my practice to use elaborate diagnostic methods such as contrast medium. Undoubtedly if the more major operation of Shirodkar is contemplated (to be followed at term by an elective Caesarean section), it is essential to be sure of the diagnosis; but with the simple procedure described no great embarrassment is caused by incorrect selection of case. It is pertinent to point out that cervical suture will not stop premature labour once the pains have commenced.

The reasons for using wire rather than nylon are as follows:

(1) The correct tension is easily obtained by means of twisting; it is impossible to tie a nylon knot with the same accuracy of tension.

(2) It is equally easy to remove the wire by untwisting; although frequently the wire has become buried in the cervix, it can always be untwisted and removed.

(3) In my opinion some of the silk and braided-nylon sutures may have a wick-like action and allow secretion from the vagina to percolate into the cervix.

(4) The wire sutures are of inestimable psychological value and this is probably their greatest asset. Once inserted the sutures impart a tremendous feeling of security to a patient who has previously known nothing but the apprehension of an impending miscarriage and the deep disappointment and despair associated with unfruitful pregnancy.

Sir Dugald Baird (Aberdeen)

I do not intend to say very much at this stage as I shall be dealing with the subject in my contribution this afternoon. I should like, however, to be just a little reassuring. We all know how difficult it is to prevent prematurity; but the number of extremely premature infants who survive and join the ranks of the mentally and physically handicapped is very small. What interests me more is that the highest incidence of mental deficiency (defined by an I.Q. of 70 or under) is in the weight group 4½ to 5 pounds. These babies are nearly all full-time by dates—they are not prematurely expelled from the uterus; it is a matter of the type of baby rather than the duration of gestation.

I for one am not particularly impressed that the obstetrician is contributing a large part to the prematurity problem. It seems to be more a genetic and sociological rather than a purely obstetric question.

Professor C. Scott Russell (Sheffield)

Professor C. Scott Russell, Sheffield, presented a 3-minute film illustrating the value of urinary pregnanediol estimation in placental insufficiency, and the successful management of a severe case.

ENVIRONMENTAL HAZARDS OF PREGNANCY

BY

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I.—WORK DURING PREGNANCY

THE effects of work during pregnancy have been studied in 1,318 primiparae, or all women who gave birth to a single first child in Northamptonshire during 1952 (Stewart, 1955). In this group there were 780 women who were described as housewives, 295 women who were in paid employment for less than 28 weeks of the relevant pregnancy (short-term workers), and 253 who went out to work for longer periods (long-term workers). Most of the working mothers were employed as seamstresses in clothing or shoemaking factories, but some worked in the retail trade, assembly work in light industry, or personal services, and a few had professional qualifications. It is not known how many of the women employed domestic servants, but judging by the husbands' occupations the proportion who did so was probably higher for housewives than for workers.

These and other facts were obtained from a recent survey which included all babies born in Northamptonshire in 1952 and sample populations of babies born in this year in four other Local Authority areas (Stewart, Webb and Hewitt, 1955). At the time of the survey a lengthy schedule was completed for each birth. Most of the facts recorded on these forms came from existing medical records (antenatal, obstetric and postnatal), but additional information was obtained by visiting the mothers in their homes 6–7 weeks after delivery. The records relating to the three groups of primiparae described above revealed the following findings.

Maternal Age and Physique

Of the housewives 42·4 per cent were over 25 years of age, compared with 26·7 per cent in the short-working group and 24·9 per cent in the long-working group. But the three groups were alike in respect of maternal physique.

Toxaemia of Pregnancy

In spite of the housewives being on average older than the workers, there were virtually no differences between the three groups in respect of toxaemia (14·1 per cent housewives, 14·4 per cent short-term workers, and 15·4 per cent long-term workers).

Social Class

Compared with the housewives, there was a deficiency of Social Classes I and II among the working mothers (20 per cent and 9 per cent respectively), but Social Classes IV and V were equally represented (26 per cent in each group).

Pre-marital Conceptions

Less than 10 per cent of the housewives conceived their babies before marriage, compared with 27 per cent of the working mothers.

Stillbirths, Neonatal Deaths and Premature Babies (see Table I)

There were significant differences between the three groups for each of these events which were only partially accounted for by the observed differences in social class and pre-marital conceptions. In each respect the housewives suffered least and the long-term workers most.

Stated Causes of Death

The only significant differences between the three groups were deaths ascribed wholly or

TABLE I

Groups	Stillbirths and Neonatal Deaths (Per cent)	Premature Babies (i.e., Birthweight 5½ pounds or less) (Per cent)	Number of Mothers
Housewives:			
Pre-marital conceptions	4·8	6·3	63
Post-marital conceptions	2·6	4·6	717
Social class I and II	1·9	2·6	156
Social class III	2·6*	4·0	421
Social class IV and V	3·9	7·8	203
All housewives	2·8†	4·7†	780
Workers (less than 28 weeks):			
Pre-marital conceptions	9·7	14·5	62
Post-marital conceptions	3·6	6·7	223
Social class I and II	—	3·3	30
Social class III	5·3*	8·5*	188
Social class IV and V	6·0	10·4	67
All short-term workers	4·9†	8·4†	285
Workers (over 28 weeks):			
Pre-marital conceptions	12·9	14·1	85
Post-marital conceptions	4·8	9·5	168
Social class I and II	—	5·9	17
Social class III	6·1*	10·4	163
Social class IV and V	12·3	13·7	73
All long-term workers	7·5†	11·1†	253

Significance Tests: †=P>0·01; *=P>0·02.

partly to prematurity. The distribution of these cases was 1·2 per cent for housewives, 1·8 per cent for short-term workers, and 4·3 per cent for long-term workers. There were only 9 deaths from congenital defects, 3 among the housewives and 6 in the working groups.

Matched Samples

In a sample of 143 mothers who worked for less than 28 weeks and a sample of 143 housewives—matched for age, social class and civic status at the time of conception—the prematurity rates were 4·9 per cent and 2·1 per cent respectively. In similarly matched samples of 152 mothers who worked for more than 28 weeks and 152 housewives, the corresponding rates were 7·3 per cent and 1·3 per cent.

CONCLUSIONS

There appears to be a genuine association between premature delivery and work during pregnancy. The findings are in line with those reported by Douglas (1950), who also showed that the association only held for working mothers who lacked domestic assistance in their homes.

II.—MATERNAL PHYSIQUE AND TOXAEMIA OF PREGNANCY

The survey records described in the last section have recently been re-examined to discover whether there is any relationship between physique and toxaemia of pregnancy. The work is still incomplete, but it already suggests that a predisposition to toxaemia is not confined to exceptionally obese women (Møller-Christensen, 1938; Biro, 1944).

In most of the survey records the mothers' physique was merely described as tall, average, or short, and obese, average, or thin—descriptions which applied to the appearance of the mother when she was visited 6 or 7 weeks after

delivery. There were, however, in the Northamptonshire sample over a thousand women whose heights and weights had been recorded at this time.

An earlier analysis of a sample of records taken from all five Local Authority areas had shown that the women who were described as short and obese had experienced more stillbirths and neonatal deaths than had women of average build, and that women who were described as tall and thin had done slightly better than average (Stewart, Webb and Hewitt, 1955).

The new work relates to 1,201 women in the Northamptonshire sample who had records of weight and height and could therefore be classified according to their build (height divided by the cube root of weight). When this was done it was discovered that 202 of the mothers were overweight for their height (body-build indices 10·8–12·0), 299 were underweight for their height (13·1–14·5), and the remaining 700 (12·1–13·0) were concentrated in the middle of the body-build scale.

Table II shows the incidence of toxaemia in these three physique groups.

According to these figures, the women who were overweight for their height had developed toxaemia of pregnancy twice as often as women who were of average weight for their height and over three times as often as women who were underweight for their height.

The table does not distinguish between multiparae and primiparae (twin births have been excluded), but a separate analysis of these two groups yielded similar results. The multiparae had, on average, lower body-build indices and lower toxaemia rates than the primiparae, but in both groups there was a steady rise in toxaemia incidence from the top to the bottom of the body-build scale (slender → obese).

It is uncertain how accurately the weights and heights were recorded in this survey, but they presumably described the mothers' physique after delivery. It is therefore of interest to know that in an unpublished series of mothers who were asked to state their pre-pregnancy weights, were weighed within 15 weeks of conception and weighed again at postnatal clinics, the relationship between body-build and toxaemia was roughly the same whether the body-build index was calculated on the basis of the earlier or the later weights (Soutar, 1958).

Conclusions

Women who are overweight for their height appear to develop toxaemia of pregnancy more readily than women who are underweight. It would be interesting to know if this tendency is due to the fact that pregnancy exaggerates a "natural" tendency to obesity in such women and whether the dietary regime recommended by Nixon (1955) is equally successful for all physical types.

III.—Antenatal X-rays

A recent survey of childhood malignancies (Stewart, Webb and Hewitt, 1958) has received so much publicity, and the findings have so often been misinterpreted, that a restatement of what the authors—as opposed to the popular press—considered to be the correct interpretation of the findings may be helpful.

During the survey mothers of 1,299 children who had died of malignant diseases before their tenth birthdays were interviewed (case group),

Table II

Weight/Height	Body-build Index ($Ht \div \sqrt[3]{Wt}$)	No. of Mothers	Toxaemia of Pregnancy		
			No. of Cases	Per cent	Relative Risk
Overweight	Low	202	46	22·6	2·03
Average build	Average	700	83	11·9	0·92
Underweight	High	299	24	8·1	0·62

also the mothers of 1,299 live children, who were matched for age, sex and locality with the dead children (control group). In this way it was discovered that 178 or 13·7 per cent of the dead children had been X-rayed *in utero*, compared with only 93 or 7·2 per cent of the live children. When the original records of these diagnostic X-ray examinations were examined it was found that 18 of the dead children and only 2 of the controls had been X-rayed in the first half of pregnancy and that 15 dead children and 2 live children had been subjected to more than 5 exposures. For X-rays not involving exposure of the survey children (including chest and limb X-rays of the mothers during the relevant pregnancy) there were only minor differences between the cases and controls. It was therefore concluded that prenatal exposure to diagnostic X-rays had appreciably increased the risk of childhood malignancies.

In the published report of this investigation rough estimates of the risk were given which were based on the percentage figures quoted above. According to these estimates children who are X-rayed before birth are

$$\left(\frac{13\cdot7\times92\cdot8}{7\cdot2\times86\cdot3}\right)$$

or twice (2·03) as likely to die of malignant diseases before the age of 10 as other children; alternatively, (13·7–7·2 per cent) or between 6 and 7 per cent of the cases included in the survey had died because they had been X-rayed before birth.

To appreciate what "doubling the normal risk" means in this context it is important to realize that the normal risk is small and that in this country only one child in 1,200 is likely to die of a malignant disease before the age of 10. In other words, only 600 of the 700,000 children born in England and Wales each year are likely to suffer this fate. As these deaths are spread over 10 years, even doubling the risk for *all* children born in a single year (i.e., X-raying every single one of them before birth) would only add about 60 "extra" deaths to the yearly total for the whole country.

Judging by the survey results, even during a period (1943–55) when obstetrical X-ray examinations were assumed to be perfectly safe procedures, less than 10 per cent of the children in this country were X-rayed before birth, and only 100 of the dead 1,299 children in the recent retrospective survey were accounted for by the X-ray findings. It is not therefore surprising that one or two obstetricians and radiologists who have attempted to check our results with a prospective survey have failed to find a single case of leukaemia among the children X-rayed in their pelvimetry clinics. Leukaemia accounts for less than half of all childhood malignancies, and not more than 1 child in 2,800 is likely to develop this disease within 10 years of birth. It would therefore be necessary to do a complete follow-up of 3,000 X-ray pelvimetries for 10 years to discover even one "extra" case of leukaemia. If this were done by two separate investigators, it would still be "as likely as not" that only one investigator would discover more than one case of leukaemia in his series.

Conclusions

We are still prepared to stand by our original statement that a "typical" X-ray examination *in utero* doubles the risk of leukaemia and cancer in childhood. The actual risk for any single examination depends on the intensity of the X-ray exposure and the date of the exposure. X-rays in the first trimester are more dangerous than X-rays in the third trimester, and two exposures are more dangerous than one.

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THE CONTRIBUTION OF OBSTETRICAL FACTORS TO SERIOUS PHYSICAL AND MENTAL HANDICAP IN CHILDREN

BY

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THE hazards of maternity which may cause death or damage to the child may be roughly divided into two groups: (*a*) abnormal intra-uterine conditions before the onset of labour, and (*b*) damage caused during labour itself. The two groups are not entirely clear-cut since neither is capable of being measured accurately and since a foetus which has been in hazard before the onset of labour may be critically affected by a degree of stress during labour which is of little consequence to a normal foetus.

Naturally, the obstetrician has made more progress in preventing the hazards of labour than of pregnancy, and with competent management birth trauma likely to cause permanent damage should be rare. He usually assesses progress in this respect by a study of perinatal deaths and is not well qualified to discuss remote effects in the survivors.

When I was invited to take part in this Symposium, I thought it might help to clarify my mind if the obstetric antecedents of a group of obviously handicapped children were investigated. Dr. Denys Fairweather and Dr. Raymond Illsley did the work, and I am grateful to them for allowing me to report the following findings.

Out of 3,370 births in a Scottish city during 1948, we were able, in 1959, to identify and investigate 64 children attending the special school for handicapped children. Of these, 7 had a physical handicap only, and 57 were educationally subnormal (I.Q. 70 or less), of whom 4 had a physical as well as a mental handicap.

Of the 11 children with a physical handicap, 4 were deaf, 2 malformed and 2 spastic; the remaining 3 suffered respectively from eczema and asthma, epilepsy and Perthes disease.

OBSTETRIC FACTORS

Prematurity

In 10 of the 64 cases (15 per cent) the baby weighed 5½ pounds or less at birth. This high incidence of prematurity suggests that low birth weight might be an important causal factor in serious mental and physical handicap. The avoidance of prematurity might thus be of great importance in cutting down the incidence of mental handicap. In practice this has proved very difficult.

Table I gives the incidence of babies of 5½ pounds or less in primigravidae (single pregnancy) arranged in three height groups and three social classes. It shows that the incidence varies from about 2 per cent in tall women married to business and professional men to 15 per cent

TABLE I
Prematurity Rates Per cent in 4,322 Primiparae

Maternal Height	Husbands' Social Class			All Classes
	I and II	III	IV and V	
Tall .. .. (5 feet 4 inches+)	1·9	3·5	7·4	4·0
Medium ..	5·3	6·6	8·5	7·0
Small .. .. (— 5 feet 1 inch)	7·7	10·5	14·9	11·7
All heights ..	4·0	6·7	10·1	7·2

TABLE II

Follow-up in 1959 of all City Prematures born in 1948

1948		1948–59		1959	
Birth Weight	Number	Died	Left City	Alive in City	I.Q. 70 or less
–4 pounds	84	50	9	25	1
–4·5 pounds ..	39	14	2	23	1
–5·0 pounds ..	61	8	12	41	6
–5·5 pounds ..	123	12	39	72	3
Unknown	3	3	—	—	—
All prematures ..	310	87	62	161	11

in short women married to men doing semi-skilled or unskilled work. A uniformly high standard of antenatal care was given to all these women. The conclusion to be drawn is that the type of patient greatly influences the prematurity rate even when a high standard of medical care is available.

Dr. Drillien has found that in babies weighing less than 3 pounds at birth 14 per cent had an I.Q. of 70 or less. Fortunately such babies are few. Out of a total of 3,370 births in the City in 1948 only 6 babies of this weight survived to about 10 years of age. Table II shows that the highest incidence of serious mental handicap occurred in the weight group 4½–5 pounds, 6 out of 41. In 48 babies weighing less than 4½ pounds there were only 2 with an I.Q. of 70 or less. This suggests that birth weight by itself is not of prime importance.

Table III gives the results of intelligence tests in 363 primiparae. In the 25 who gave birth to premature babies, there is, on the null hypothesis, a striking excess of women of low intelligence. Also of great interest is the fact that only when the baby is 7½ pounds or more is there a clear excess of mothers of superior intelligence and a deficiency of those of lower intelligence.

TABLE III

Birth Weight and Intelligence of Mothers
(Expected numbers in each intelligence group in brackets)

Mothers' Intelligence Test Score*	Premature		All Premature	Mature		All Births
	–4½ Pounds	4½–5½ Pounds		5½–7½ Pounds	7½ Pounds–	
Good	0 (2·1)	1 (5·3)	1 (7·4)	60 (63·6)	46 (36·0)	107
Average	4 (2·7)	7 (6·9)	11 (9·6)	79 (85·1)	53 (48·4)	133
Poor	3 (2·3)	10 (5·9)	13 (8·2)	83 (73·2)	27 (41·6)	123
Totals	7 (7·0)	18 (18·0)	25 (25·0)	222 (222·0)	126 (126·0)	363

* Wechsler-Bellevue verbal scale.

TABLE IV

Distribution of Premature Babies by Mothers' Intelligence and Height

(Expected numbers in brackets)

Mothers' Intelligence Test Score*	Mothers' Height			All
	Tall	Medium	Small	
Good ..	– (2·8)	– (3·4)	1 (1·2)	1 (7·4)
Average ..	1 (2·0)	5 (5·6)	5 (2·0)	11 (9·6)
Poor	1 (3·0)	6 (4·0)	6 (1·2)	13 (8·2)
All	2 (7·8)	11 (12·8)	12 (4·4)	25 (25·0)

* Wechsler-Bellevue verbal scale.

Table IV shows that when the mothers of the 25 premature babies are arranged in three height groups there is a striking deficit in the number of tall women and an excess in the number of small women. In addition it is clear that the excess of women of under average intelligence is greatest in the small women. These findings are supported by some facts about the 10 mothers of premature children born in 1948 who are being educated at the special school for handicapped children in the City. Five of the 9 mothers where the height was known measured 5 feet or less. Five of the pregnancies were full-time by the date; one terminated at 37 weeks, 2 more prematurely and in 2 the duration of the pregnancy was uncertain, but both babies weighed more than 4 pounds.

Intelligence tests performed at the age of 9 in all premature babies born in 1948 in the City and still resident there show that at birth weights between 4 and 5½ pounds the average I.Q. was much lower in those born at or near term than in those where delivery occurred at 36 weeks or less. A foetal weight of 5 pounds at 36-weeks gestation suggests a normal rate of growth, whereas at 40 weeks it may represent a serious disturbance of intra-uterine nutrition and growth.

We can therefore conclude that while extreme prematurity may result frequently in serious mental handicap, there is no clear indication that within wide limits premature expulsion from the uterus does the foetus any serious harm.

Babies weighing between 4½ and 5½ pounds cannot be regarded as very premature; indeed, many of them are born at or near term; yet this weight group contains the highest proportion of babies with a low I.Q. This cannot be explained on a pure weight basis. Probably there is a genetic factor—since many of the parents also have a low I.Q.

Intra-uterine growth is poor and the deleterious effect of these factors on the intelligence test performance at the age of 9 is reinforced by a poor social environment after birth.

Abnormal Pregnancy or Labour

Investigation of the obstetric records showed that in 57 cases the pregnancies and labours were, for practical purposes, perfectly normal. In only 7 out of the total of 64 cases investigated was there any obvious abnormality of pregnancy or labour, and in only one of these was there an undoubted causal relationship with the eventual fate of the child (Table V). One spastic child sustained cerebral damage during a difficult forceps delivery undertaken because of disproportion. One educationally sub-normal child was seriously in hazard during pregnancy; it weighed less than 5 pounds when delivered at 38 weeks because the mother developed severe pre-eclampsia; the delivery itself was short and easy. In 5 cases the abnormalities of pregnancy and labour were not severe or unusual, and there seems no reason to believe that the children were permanently damaged by them.

SOCIAL FACTORS

The association between low birth weight, mental handicap, small stature of the mother and low social status has already been pointed out. Even in the 7 cases in Table V, where there was a possible obstetrical cause for the handicap in the child, adverse social circumstances and poor heredity were also prominent. Five of the fathers were in unskilled occupations and 4 of them had unstable job histories, or prolonged spells of unemployment, or were disabled. In 4 cases also, the child had had relatives at the special school or some of its siblings were described as "backward". Since these findings are very similar to

TABLE V

Seven Educationally Sub-Normal Children Where Possible Obstetric Factors Were Found

Obstetric History	Fathers' Occupation	Relatives at Special School
1. Primigravida, age 25 Admission at 41 weeks, ante-partum haemorrhage Foetal heart rapid in labour Spontaneous delivery, 5 pounds 15 ounces Resuscitation needed	General dealer (Many jobs)	1 uncle 3 cousins
2. Para-1, age 30 Pregnancy normal, 38 weeks Foetal heart rapid, irregular Caesarean after 4 hours, 7 pounds 8 ounces Breathing delayed 10 minutes	Labourer (Many jobs, unemployment)	—
3. Primigravida, age 20 Pregnancy normal, 43 weeks 2nd stage 90 minutes, spontaneous delivery, 6 pounds 9 ounces Cried fairly quickly	Labourer (Many jobs)	2 cousins 1 second cousin (2 siblings "slow")
4. Primigravida, age 19 Pregnancy normal, 40 weeks Foetal heart slow, meconium, 2nd stage Spontaneous delivery, cord round neck, 6 pounds 12 ounces Resuscitation ++	Labourer (Often unemployed)	2nd cousin
5. Primigravida, age 21 Threatened abortion, 5 months Easy normal labour at 41 weeks, 4 pounds 9 ounces	Storekeeper (disabled: unemployed 2 years)	Sister (2 siblings "backward")
6. Para-3, age 28 Severe pre-eclampsia, 38 weeks Very short labour, 4 pounds 14 ounces	Parcel porter	—
7. Primigravida, age 28 Normal pregnancy Contracted pelvis, very difficult, forceps Resuscitation ++, 7 pounds (spastic)	Foreman plater	—

those in which no obvious obstetrical factors existed, all 53 cases of mental handicap will be considered together from the sociological point of view. The majority of the parents are in Social Classes IV and V, the semi-skilled and unskilled working classes. Most of the mothers began their reproductive lives at an early age, an unusually high proportion of them with an illegitimate child.

The parents came from large families which have been unusually prolific. Thus, the 53 mothers have 216 live siblings, 42 per cent of them coming from families of 7 or more children. Of the 216 siblings, 162 have married and have had a total of 529 live-born children (3·26 children per sibling); many of them have not yet completed their families. Of the mothers with whom we are immediately concerned, 50 are married and have had 242 children (mean family size 4·8), and their reproductive lives are by no means over. To complete this aspect of the story, it has been ascertained that 51 grand-parents, about whom it was possible to get accurate data, have *so far* given rise to 782 grandchildren.

Of the 53 immediate families, 19 seemed to

be more or less "normal", in the sense that the domestic circumstances were not unusual in any way and the fathers were in stable employment (see Table VI). Three of the children were

TABLE VI

Parents of 53 Educationally Sub-Normal Children Born in 1948

Child illegitimate	3
Family: alcoholism, delinquency, marital fights	2
Father died	5
Father deserted family	2
Father unemployed for at least one year	13
Father: unstable job history	9
Father in stable employment, family "normal"	19
	53

illegitimate. In 2 of the families there was a history of alcoholism, delinquency and marital fighting. Five of the fathers had died, 2 had deserted their families, 13 had had spells of unemployment lasting at least one year, and 9 had notably unstable job histories.

A striking fact, which we have not been able to work out in detail yet, is that many of these families are inter-related.

In 30 out of the 53 cases, the parents had both been born and brought up in the City, so that full information could be obtained about the "extended" families. In 18 of these 30 families, the children with which we are concerned had close relatives who also attended the special school. In every respect, except that of illegitimacy, those with relatives at the special school were socially inferior to those without affected relatives (Table VII).

TABLE VII

Families of 30 Educationally Sub-Normal Children Born in 1948
(Both parents reared in the City)

Characteristic	Relatives at Special School	
	Yes	No
All cases	17	13
Long-term unemployment	8	1
Living in slum or clearance areas	12	3
At least one child illegitimate	2	4
Unstable marital or occupational history	13	3
Child's I.Q. under 60	10	3
Mother's height under 5 feet 1 inch	11	3

The 64 children attending the special school do not constitute all the children with a severe physical handicap and an I.Q. of 70 or less born in that year. A few are being educated at the normal day school, but it is unlikely that their inclusion will make much difference to the general conclusion that obstetric hazards play a small part compared to genetic and environmental factors in causing serious physical and mental handicap.

It is, of course, possible that obstetric hazards can cause minor degrees of damage which, if widespread, would be of great practical importance especially in this scientific age. The practical obstetrician will be particularly interested to hear from Dr. Fraser whether the varying degrees of asphyxia which still occur frequently cause permanent disability. On the answer to this question may depend future trends in management of labour and in methods of resuscitation of the newborn.

THE RESIDUAL EFFECTS OF NEONATAL ASPHYXIA

BY

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AND

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IN number and variety, the conditions which have been stated to follow asphyxia at birth are more than impressive: a full list would be tedious, for it would have to include many major and minor handicaps, both of body and mind. Unfortunately the evidence is often unsatisfactory or incomplete. Much of it is based on retrospective studies, with their unavoidably limited value. Some of the follow-up studies have had inadequate controls or none at all, and certain investigations, in spite of being broadly similar, have produced quite opposite results.

However, the material selected for study has varied greatly, and this may explain a good deal of the contradiction. To take one example, Usdin and Weil (1952) excluded from consideration infants in whom intracranial haemorrhage had been diagnosed or even suspected, those with abnormal neurological signs either at birth or in later childhood, and even those delivered by Caesarean section, while other authors (Craig, 1950; Hellström and Jonsson, 1953) have deliberately chosen babies whose early clinical behaviour suggested cerebral damage. Reports which have such different starting-points are not conflicting so much as complementary.

From this extensive and confusing literature (Graham *et al.*, 1957; *Lancet*, 1957; Illingworth, 1958; Bailey, 1958), certain overall impressions have been derived. It is clear that instances of serious defect do occur after neonatal asphyxia—cerebral palsy, epilepsy, mental retardation and behaviour disorder, sometimes in combination—and that the association is not only with mechanically difficult births. Some of those children who escape obvious handicap are believed to have minor forms of physical or mental impairment. On the other hand it is generally held that, even when asphyxia has been severe, the majority of surviving infants develop normally, without any defect (Illingworth, 1955). There is need of further study, both of the exact sequelae and of the clinical circumstances which give rise to them, and several long-term follow-up projects are at present going on. It is about the progress of one of these in Aberdeen that we are able to offer an interim report.

Asphyxia neonatorum, of course, is by no means a homogeneous condition. It is a conglomerate, with many diverse causes from contracted pelvis to ante-partum haemorrhage, and the effects of these on the baby may well be different. Forecasting the outcome of particular cases is not likely to become easier, for presumably impairment must depend, not only on the nature and severity of the asphyxiating process, but on differences in susceptibility between individual infants.

DEFINITION

In our hospital records the infant is classified at birth into one of four grades, and a written

description is demanded under such headings as Muscle Tone, Cry and Response to Resuscitation. It is this background of recorded detail which has made it possible to select cases for follow-up and to designate them as moderately or severely asphyxiated. It is an overall clinical assessment, in which attention is paid to colour and tone, but the principal criterion is delay in the onset of regular respiration and cry (Craig and Fraser, 1957).

TABLE I
Degree of Neonatal Asphyxia

Delay Before Onset of	Asphyxia "Moderate" (minutes)	Asphyxia "Severe"
First gasp ..	0– 3	Usually 3–5 minutes
Regular respiration	3– 5	More than 5 minutes
Cry	5–15	Usually 15 or more 15–30 minutes or longer

To interpret what we mean in this project by the terms *moderate* and *severe*, composite descriptions have been worked out (Table I). It will be seen that while our "moderate" infant might gasp at birth, he did not establish regular breathing for 3 to 5 minutes. In "severe" cases regular respiration and cry began usually in 15 to 30 minutes. Some infants took longer but the group as a whole is not one in which asphyxia was extreme.

SELECTION OF CHILDREN

Infants with moderate asphyxia are in ample supply and all 60 children in this group, with their paired controls, have been examined at the same age of 7½ years. To collect an adequate number of the severely asphyxiated it is necessary for us to examine them at different ages. Of the 40 pairs in this group, 23 were aged 7½, 8 were aged 10½, and 9 pairs were aged 11½ years; this fragmentation hinders the analysis of some of our results at the present stage. Ultimately the severe group will be the larger. The causes of asphyxia may alter over a period of years, reflecting changes in obstetric practice. In half of the older children, born in 1947–48, the asphyxia could be firmly attributed to mechanically difficult birth. Among the 1950–51 births, as would be expected, the proportion of asphyxia due to physical trauma appears to have declined. It is with non-mechanical causes of severe asphyxia that we are at least equally concerned.

We have not excluded infants with intracranial haemorrhage, because we are not convinced that a division of this kind of material into haemorrhagic and anoxic cases is either justified or practicable. What we are studying, therefore, will not be described as the results of "anoxia", or for that matter of "apnoea". We prefer to retain the term "asphyxia" and use it to indicate infants who suffered *delay in the establishment of satisfactory respiration*; the reasons for this were varied and in many cases multiple.

It was considered necessary to exclude three types of infant—prematures (by the rough but convenient method of using birth weight), twins and illegitimates. Each child in the asphyxiated group has a control whose condition at birth was excellent. Matching of controls was by sex (among asphyxiated infants, boys outnumber girls by 3:2) and by birth-rank; in our series two-thirds of the children are firstborn. The important factors of birth-weight, social class and maternal age were not matched for, but we find good agreement in these respects between the asphyxiated and control groups. Every infant was born in Aberdeen Maternity Hospital and the family had an Aberdeen City address at the time. Of the children selected for follow-up fully 80 per cent are being examined, failures to attend being mainly due to migration.

EXAMINATION

Each child attends twice, with an interval of two weeks between the visits, and is examined for a total of 4½ hours. Assessments both by paediatrician and psychologist are comprehensive, but we lay particular emphasis on the objective measurement of personality, perception and motor co-ordination. Thus the persistence and perseveration and distractibility of each child are measured by standardized tasks which yield numerical results (Eysenck, 1953). Many tests had to be adapted for young children and some were specially devised; it will be possible to mention only a few of them.

There is one question which a project of this nature is especially fitted to answer: Assuming that a minority of asphyxiated infants sustain obvious residual damage, what happens to the others? Are they quite unaffected, or is minor impairment of one kind or another a frequent occurrence? Since the difference between normal individuals is so great, it is only by comparing the abilities of groups of children that minor degrees of impairment can be detected. If the hypothesis is correct that there is a gradient of foetal damage (Lilienfeld and Pasamanick, 1955), we should throw light on the lower end of the continuum, and in theory we might expect a gradation in some of our results from the severe group to the moderates to the controls.

This is a progress report and all results at this stage, negative as well as positive, must be regarded as provisional.

Neurological Disorders

There is no difference as yet between the two groups in the incidence of defective vision, squint, hearing loss and speech disorders. One child has cerebral palsy and another has residual handicap from an Erb-Duchenne brachial palsy; both of these were severely asphyxiated at birth. One girl who would have been included was found to have died in status epilepticus at the age of 5 (Table II). The one spastic child has focal epilepsy also. Three others are suspected of epilepsy; all are reported to have abnormal electro-encephalographic records. All of these 5 children with fits were asphyxiated at birth. Since epilepsy is sometimes late in appearing, its true incidence will be found only by following this material for a longer period. Analysis of EEG records from a proportion of our severe group, by a neurologist who is unaware of their birth-history, will be available later.

In Cases 1, 3 and 4 of Table II, scrutiny of the hospital records shows no adequate explanation for the severity of their asphyxia. This gives point to an old suggestion, that some infants may behave in an asphyxiated manner at birth because of intrinsic defect or because of brain damage sustained during foetal life—the asphyxia then being a result of neurological abnormality rather than the cause of it. Such cases must be few, but certainly asphyxia does sometimes occur without any perinatal reason being apparent.

Table II

Occurrence of Epilepsy

	Neonatal Asphyxia
Definite:	
1. Grand mal from age 1; died at age 5	Severe
2. Myoclonic seizures; cerebral palsy	Severe
Probable:	
3. Ten short fits, from age 8 to 10	Severe
Possible:	
4. Four fits at age 1 and one at age 6	Severe
5. Three fits at age 6	Moderate

Motor Ability

A relevant point from the early history is the age at which the child first walked, which can be fixed with considerable accuracy by reference to health visitors' record cards. Leaving out of account the spastic child, who could not walk alone until he was 5½ years old, there is a difference in Table III between the 99 asphyxiated children and their controls ($P<0{\cdot}05$). The apparent gradation of the three means is not at present significant.

Table III

First Walked Without Support
(Age in Months)

	Mean	Range
98 controls	13·0	9–20
60 moderately asphyxiated ..	13·4	10–19
39 severely asphyxiated ..	13·9	11–22

When locomotor co-ordination is to be objectively measured, one method is Heath's (1942) rail-walking test. The child walks barefooted, heel to toe, along a series of three low wooden rails. Complete success would yield a score of 153 (Table IV). The boy with cerebral palsy could not do this at all. Leaving him again out of consideration, there is a significant

TABLE IV
Heath's Rail-walking Test

	Mean	Range
At 7½ years:		
83 controls	67·6	26–128
83 asphyxiated	61·9	8·5–102
At 10–11 years:		
17 controls	90·8	39–135
16 asphyxiated	73·4	34–117

difference ($P<0·05$) between the asphyxiated and control groups; this is consistent and cannot be explained by inferior performance of a few individuals.

For measuring manual dexterity, the method we first selected is the R.V. test (Vincent, 1955) in which the child has to pick up ball-bearings one at a time and drop them into a slot, the score being the time taken to deal with 44 balls. The difference so far observed between the two groups is not significant. As with most tests of dexterity, performance here depends on speed as well as on precision. These are separate facets of motor ability, however, and are not closely related; we are therefore now using tests intended to measure each in isolation from the other. Eight children in the asphyxiated group showed slight intention-tremor, compared with one of the controls. This was almost always of minimal degree, but it may be a clue to impairment of manual precision.

INTELLIGENCE AND ATTAINMENTS

There are no convincing differences at present between the two groups in intelligence (Wechsler, 1949), reading or arithmetical ability. Five of the children are mentally defective, and 2 of these are controls.

PERSONALITY

Behaviour disorders of two kinds have been reported to occur with increased frequency in children who were asphyxiated at birth. The broad distinction is between, on the one hand, emotional disorders or neuroticism and, on the other, hyperkinetic behaviour of organic origin. This consists chiefly of restlessness, impulsiveness and distractibility, making up the so-called hyperkinetic behaviour syndrome, which is believed to arise from brain-damage in early life (Laufer and Denhoff, 1957). Nine children in our asphyxiated group have at some time been knocked down in the street, but only 2 of the controls. If this should prove to be a genuine difference, impulsiveness would be a possible explanation.

Behaviour is being assessed by a considerable battery of objective tests, capable of demonstrating small differences. During these, and throughout his work, the psychologist is unaware of the birth-history of the child in question. A personality rating scale is also completed by the mother and independently by the school-teacher; it consists of thirty-six questions, each with five descriptive ratings to choose from. We have therefore searched with care for discrepancies in the field of personality between the asphyxiated and control groups, but have not as yet found any convincing difference.

PERCEPTION

Disorders of perception have frequently been described as residual effects of brain-damage in infancy. We are using several perceptual tests, and one of these is a figure-background test adapted from Strauss and Lehtinen (1947). It consists of 18 pictures, of simple objects seen against backgrounds such as wavy or zigzag lines. Each picture is flashed twice on a screen, for exposures of ¼ second, and the child is asked to say what he saw. A correct response is taken to be one in which the figure is correctly named and no mention is made of the background. Characteristically the brain-injured child is said to have his attention diverted to the background, so that he refers to this and may omit the figure or name it incorrectly. A probable difference between the groups has been detected; in one category of response, i.e., objects incorrectly identified, the difference is strongly significant ($P<0·01$).

CONCLUSION

In summary, then, what can be said about results at this stage? We have carried out a lengthy and careful examination of children who were asphyxiated at birth, and in particular of

40 whose asphyxia was severe, having made no important exclusions except that of babies under 5½ pounds in weight. Few of the children have obvious defects, and some of those may not be causally related to anything which happened at the time of birth. The picture is therefore broadly reassuring from the obstetrician's point of view, but we must add three reservations: (1) The findings are tentative and incomplete. (2) If one were to collect an adequate number of children who had had gross intracranial haemorrhage or asphyxia of extreme severity, the status of this small minority might be found to be different. (3) We have provisional evidence that minor impairment is relatively common. If this is so, it will have to be reckoned with, since frequency lends importance even to lesser degrees of damage.

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COMPLICATIONS OF PREGNANCY AND NEUROPSYCHIATRIC DISORDER

BY

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TIME limitations force a rather abrupt introduction to our subject of the relationship between prenatal and paranatal factors and the outcome of pregnancy. The association of foetal and neonatal deaths due to central nervous system damage with complications of pregnancy, and a study of New Haven Negro infants (Pasamanick, 1956) which indicated that favourable prenatal factors, nutritional as well as other, were probably responsible for a growth and developmental pattern comparable to that of white infants, led us to work in this area. One of the major hypotheses developed is that there exists a continuum of reproductive casualty related to abnormalities of pregnancy consisting of a lethal component resulting in foetal and neonatal deaths and a sub-lethal component resulting in various degrees of neuropsychiatric disability. Depending on the degree and the location of the damage, these disabilities range from the more overt abnormalities of cerebral palsy (Lilienfeld and Pasamanick, 1955), epilepsy (Lilienfeld and Pasamanick, 1954), and mental deficiency (Pasamanick and Lilienfeld, 1955) down through the lesser disabilities consequent to cerebral disorganization secondary to minor degree of damage and producing such entities as behaviour disorders (Rogers, Lilienfeld and Pasamanick, 1955), reading disabilities (Kawi and Pasamanick, 1958) and tics (Pasamanick and Kawi, 1956).

To date these six clinical entities, plus speech disorders in childhood (Pasamanick, Constantinou and Lilienfeld, 1956), have been investigated in a series of retrospective epidemiological studies. The basic design in all seven is similar and all but one were done in Baltimore, Maryland. Cases with the particular condition under study were selected from the rosters of clinics, hospitals, schools, or institutions, and an appropriate matched control selected, taking into account socio-economic and other variables which might affect the conditions being investigated. In the behaviour disorder study the control was the next child alphabetically of the same sex in the same class as the case. In the other studies the control was the next infant of the same sex in the birth certificate register surviving the neonatal period, who was born in the same hospital to a mother of similar race and age. Hospital records were abstracted and the cases and controls compared for the incidence of complications during pregnancy and for the neonatal condition of the infant. Since hospital charts often suffer from deficiencies in recording, demonstrated differences between cases and controls would be minimal. Any bias created by the possible inclusion of cases with neuropsychiatric abnormality in the control groups, since no patients were examined, is against the hypothesis.

The findings indicate that there is a statistically

significant increase in the number of abnormalities in the cases as compared to the control infants. There is a direct relationship between the extent of the difference and the apparent severity of the clinical condition which becomes less as there is increasing opportunity for dilution by socio-cultural factors. In descending order cerebral palsy, epilepsy, mental deficiency, behaviour disorders, and reading disabilities are related positively to pregnancy complications, prematurity, and abnormal neonatal conditions. Tics are related to complications but not to prematurity and speech disorders, when unassociated with other neurological and intellectual defects, are not related to any of these abnormal conditions. Contrary to common belief, those conditions associated with the later development of neuropsychiatric disability are not the mechanical and operative difficulties, but rather prematurity and the chronic and probably anoxic complications such as bleeding during the third trimester and toxaemia. Zeman (1959), of our Division, has several cases with anatomical evidence of brain damage due to uncal herniation at birth which are analogous to Penfield's findings in cases of temporal lobe epilepsy (Earle, Baldwin and Penfield, 1953). Since the physical forces capable of producing such herniation are common to both normal and abnormal deliveries, additional explanations for the development of this condition are needed. Dr. Zeman also has evidence to indicate that this condition occurs primarily in brains that have been subjected to pathological foetal conditions such as oedema secondary to the chronic anoxic conditions of toxaemia or bleeding, and to immaturity. This may help explain why, when these complications are removed from our series, there is no significant difference in the incidence of operative procedures or other abnormalities of labour and delivery between the cases and the controls.

It is well known that neuropsychiatric disabilities in most countries are more common in the lower socio-economic groups. Other epidemiological studies that were carried out concurrently in Baltimore indicate that at least a partial explanation can be found in the fact that there is also a socio-economic distribution of the complications of prematurity (Rider, Taback and Knobloch, 1955) and bleeding and toxaemia (Pasamanick, Knobloch and Lilienfeld, 1956). As one goes from the white upper through the white lower to the non-white economic groups, the percentage of abnormality increases, the ratio being 2 to 3 to 5 for prematurity, 1 to 2 to 4 for puerperal complications, and 1 to 3 to 10 for total complications, including those associated with but not dependent upon pregnancy. These findings, which are in general contrast to reports of some British workers, would tend to indicate that there are, in actuality, wider variations between the socio-economic groups in the United States than are found in other countries.

Additional stress factors which are influenced by socio-economic status also have been demonstrated to be aetiological in the United States. For example, it has been shown that the increased admission rate to a state school for mentally defective children born in the first quarter of the year (Knobloch and Pasamanick, 1958) can be explained by the yearly variation in summer temperatures, the rates for those years following hot summers being significantly higher than for the years following cooler summers. Among the possible explanations, in addition to the stress of heat, may be a lowered protein intake which is also implicated in the socio-economic associations previously mentioned. Furthermore, a seasonal variation in those complications of pregnancy (Pasamanick and Knobloch, 1958) already demonstrated to be associated with neuropsychiatric disabilities, namely bleeding and toxaemia, has also been found, again with higher rates in the winter months.

Further operation of the continuum can be demonstrated by variation in birth-rates with season, geography, and social class (Pasamanick, Dinitz and Knobloch, 1959). A drop in the birth-rates in the spring months, that is following summer conceptions, may be explained, at least in part, by a decrease in conditions favourable to intercourse and conception as well as by an increase in foetal death-rates. These variations are also associated with conditions apt to produce stress and are found in those groups less able to counteract the effects of heat-stress, namely those in the lower socio-economic

groups and those living in parts of the country where the summers are exceedingly hot.

This has been a bare outline of a series of investigations forging new links in a chain of evidence which consistently supports a series of hypotheses relative to aetiological factors in the development of neuropsychiatric disability. It has pointed out inter-relationships between socio-cultural and biological factors which appear to have important effects on neuropsychological functioning. Retrospective studies such as these, however, merely indicate associations and point to leads for further investigations. In order to demonstrate causality, anterospective longitudinal investigations are helpful.

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GENERAL DISCUSSION

Professor B. S. ten Berge (Groningen)

Reflexes of the Newly-Born Child with Brain Lesions

Many of you will have been struck by the fact that the movements of newly-born infants differ from case to case. When observing children with possible birth trauma after an artificial delivery or who have suffered from asphyxia before or after birth, one sometimes notices such differences with striking clarity. One child lies more quietly than is normal, cries little, has feeding difficulties due to slow reaction; another child seems more lively, possibly showing signs of nervousness. With children of the latter kind also, feeding is made difficult through hyper-irritability. These rough general observations are inadequate, however, to permit an interpretation or a prognosis. The abnormal reaction often disappears after a few days, but still the obstetrician remains in doubt about the child's future. On these vague grounds, I found Dr. Prechtl willing to observe the children in the baby ward at regular times for several years.

Dr. Prechtl proceeded systematically. He made regular notes of the abnormalities in the reflexes of newly-born children after difficult deliveries and asphyxia. Over 250 neonati were examined extensively. The children were re-examined after 2–4 years to find out whether the abnormalities noted shortly after birth could be regarded as proof of brain lesions which would become more marked later on.

Of 119 children, 48 per cent showed neurological abnormalities as neonati, and 52 per cent did not. The later examination of the pathological group showed lasting abnormalities in 68 per cent. Of the normal group 8 per cent were found to have abnormalities at follow-up examination. This difference is significant at the 1 per cent level. Of the children with prenatal and paranatal anoxia, determined on clinical grounds, 52 per cent showed abnormalities at after-examination, while the group without hypoxia showed abnormalities in 17 per cent (1 per cent level significant). Seventy per cent of the neonatal pathological group showed abnormalities at age 2–4 years, namely sleeping disturbances, concentration disturbances, instability of mood, etc. Of the group of seemingly normal neonati, these abnormalities occurred in 38 per cent at 2–4 years.

Professor ten Berge then presented Dr. Prechtl's film demonstrating normal and pathological reflexes in the newborn.

Professor James Walker (Dundee)

The Organizing Committee of the Congress is to be congratulated on the choice of subject for the opening day and on the fact that speakers from a very wide range have been selected. At this time, knowledge in this field is fragmentary, the information available is incomplete and its interpretation is fraught with great difficulty. It is, however, imperative that our scanty knowledge be reviewed and sensibly assessed so that emotion and muddled thinking do not continue to cloud the issue. I cannot stress too strongly that all individual findings are in fact correct; apparently gross contradictions in series from different workers should encourage each group to discover the real reasons which promote the apparent differences. The reasons may lie in case-material, techniques or interpretation.

In my short obstetric life I have experienced much change in clinical emphasis. I began in an era of pre-occupation with maternal death; I grew up obstetrically in the period after the second world war when the study of stillbirths and perinatal mortality became our prime interest. We have now become acutely interested in the physiology of the foetus and out of this interest in foetal development we have come,

fully a hundred years after Dr. Little, to look for the real causes of physical and mental abnormalities in children. We must look very widely and very thoroughly. Each study must be conducted with the highest degree of technical skill; we must, in general, scan the whole problem and consider all possible aetiological factors be they social, genetic, biochemical, anoxic or traumatic. Likewise we must in time take into account all degrees of aberration.

Dr. Reid has beautifully introduced the problem as seen by the practising obstetrician. He has outlined the situations where we are fearful of the risks to the child's future. He has rightly stressed the importance of the acute anoxic episode, an episode which is often unrecognized by the attendant. These babies are not necessarily born asphyxiated. He reminds us that as obstetricians we are responsible for the risk to the foetus of intercurrent illness in the mother and of intercurrent therapy in the mother. We must make it our business to be informed of and to advise on all surgery and surgical investigations in pregnancy and especially to supervise the use of potent drugs like cortisone, thiouracil and chlorthiazide. He reminds us of the high standard we must bring to the care of women in labour and that we must be prepared to re-learn the skills that we have perhaps forgotten in the heyday of radiological pelvimetry. I would agree with his definition of prolonged labour—twenty hours of true labour should be adequate—but when does true labour begin? Is there a prodromal period of labour? What is false labour? This latter diagnosis can be made only in retrospect. I am very pleased to see that the intelligent use of axis-traction forceps has come back into its true place in our practice.

It is easy to criticize. Since I must raise points in discussion I crave the forgiveness of our speakers. I am certain that many of my comments will be only too obvious to them.

Dr. Drillien has suggested that the current definition of prematurity has, in research studies at least, outlived its usefulness. Foetal mortality figures, and now Dr. Drillien's findings, show that the risk to the baby appears at birth weights under 4 pounds. Sir Dugald Baird, however, has suggested that the 4½–5 pounds mal-grown baby is also an important group. So, in fact, we are rather where we started. Is the baby under 4 pounds at risk because of its weight, its gestational age or its stage of maturation? Is the risk mainly before, during or after birth? Are some of those babies delivered too late in the course of a complicating disease like pre-eclampsia when earlier intervention could have saved them? Why do we always ignore the *stillborn* premature in prematurity statistics? I have often wanted to think that such babies are a different clinical problem but it is really only a question of degree.

As far as premature labour is concerned, is it not true that the clinical cause, if not the mechanism, can often be discovered if a thorough search is made? Professor Shedden Adam has introduced us to psychogenic causes. I myself have been recently impressed by a short series where malformed uteri were responsible.

Is cerebral palsy a disease? We know now that it is a heterogeneous group of syndromes of multiple aetiology. Surely they should not all be discussed together. As a group, cerebral palsy is statistically no respecter of social class and maternal age. The various syndromes have, however, clear social gradients and are really different conditions with different aetiology and pathology. Dr. Drillien has shown how little I.Q. and physical defect can be correlated. As with cerebral palsy, so with deformity. We must learn how to sub-group conditions which are at the moment apparently homogeneous. In some instances, hydrocephalus is transmitted as a sex-linked recessive characteristic but this does not apply to all hydrocephalus. The brilliant discovery of chromosomal aberration in mongolism does not clearly label all mongols as due to primary faults in the maternal ovum. Moreover, aberration at the stage of polar body differentiation could have multiple causes. Anencephaly has been shown in Scotland to have a strong social class gradient—is this a nutritional or a genetic correlation? Could I raise a doubt, and this is a personal doubt, about the validity of the paired-case method of selecting controls? The control is selected because ideally it is identical with the abnormal except for the problem under review. The

control might, however, of itself have some other, often unrecognized, abnormality producing the same aberration as the case under study, since rarely has a defect a single cause.

Dr. Drillien has shown us that undue prematurity predisposes to mental retardation but that prematurity accounts for only a small percentage of all retarded children. What anomalies are responsible for the others? In this respect Sir Dugald Baird emphasizes the strong social gradient in his sample of mentally dull children. He has eliminated prematurity and difficult labour in his series but are we yet entitled to make the jump to a genetic cause? He has shown that dullness has bred dullness but we must assess the risk and how many other reasons there may be. How can dullness be transmitted? What is the chromosomal or gene aberration that allows a dull and a brilliant child in the same family? We have also heard of the inadequate development in childhood of cases in the poorer social groups. Is this environmental or genetic? Is the potential of those children not adequately exploited because of environment?

Dr. Knobloch has told us of the importance of prospective study without which inadequate information is gained, and during which new techniques are developed. This latter value is never to be forgotten; if you start a new programme, you must learn new techniques. Dr. Stewart has underlined the strong social factors important in the outcome of the pregnancy. We must search for the mechanisms by which those factors operate. We are interested in the problem of the short, obese woman but how accurate is a blood pressure reading in a short fat arm?

As obstetricians we have to face this new challenge since in great part we really carry the responsibility. We must bring a clinical obstetric outlook to the field. We must, for example, ask: what is the risk to the baby in severe pre-eclampsia, or accidental haemorrhage, the baby with the cord round the neck, or with inadequate growth, the premature twins? Dr. Fraser's work has outlined for us the risks to the premature baby born alive but asphyxiated. How can we as obstetricians so alter our techniques to obviate or minimize those risks? When does damage occur to a baby? Does it occur at the time of the threatened abortion, with the subsequent accidental haemorrhage or in the first few days of life after premature birth? Has it arisen in genetic change somewhere in the ancestors?

In the future our Departments must become "Divisions of Human Reproduction". We must open our clinics, our wards and our delivery rooms to trained men and women from many disciplines. There are at this moment many brilliant but unco-ordinated studies existing even in our own Universities that we must seek out and channel into the human field. Conversely, we have much to learn from animal experimentation, in methods but also in obtaining information which can be acquired only from highly controlled experiments. We might firstly try to study thoroughly the pattern of normal reproduction before venturing into the abnormal. How much do we really know about the behaviour and abilities of the normal child? What, in fact, is a normal child? How long do we have to wait before we know he is normal? Most parents will tell you that at 7 children are just impossible, as teenagers they are uncontrollable, and assessment of university entrants by skilled observers seems to be equally misleading. Perhaps we make our decisions on normality much too soon.

MR. FRANK STABLER (Newcastle-upon-Tyne)

THE point I want to raise is a small one but I think it is important, for it is a fallacy which pervades a great deal of socio-medical conclusions. It arises out of Dr. Alice Stewart's paper. I do not quarrel at all with the content of her paper which was altogether admirable and, if I may say so, her delivery of it was delightful. It is with the conclusions drawn from her investigation. She stated that attempts during pregnancy to combine housework with paid employment are liable to increase the risk of premature birth and consequently of stillbirths and neonatal deaths. I think that is a fallacious conclusion, for this reason. People who try to carry on paid work in the last 3 months of pregnancy are of the lower social groups or, as I prefer to call them, poorer

people. And poorer people have many characteristics which are not possessed by richer people and they lack many characteristics that are possessed by richer people; it might well be that any of these other characteristics might cause the effect that we see.

One can point out, for instance, that in the last 50 years the incidence of cancer has increased *pari-passu* with the decline in the wearing of top hats, but it does not follow that it is because of that. And if one takes it that poorer people enter and remain in the poorer classes partly from deficiencies of intelligence and largely from lack of discipline of any sort, any one of those factors might have caused this same result. For instance, the poorer people eat more carbohydrate and less protein; they drink more beer, they go to the pictures more frequently, they bathe less frequently. In fact I am sure that, if Dr. Alice Stewart had made enquiries of those women who had this characteristic of increased risk of premature birth and consequently of stillbirths and neonatal deaths, she would have found a direct correlation between the fewness of the baths they took and the more frequent baths of other people. If finally it is claimed that it seems sensible—it appeals to our reason—that it is a bad thing to work during the last 3 months of pregnancy, then that is begging the question. It does not follow that this particular point is the one which produced the premature births and hence the increase in foetal mortality.

DR. ALICE STEWART (Oxford) (*In reply*)

I ALWAYS feel that on these occasions all the well-known quips about statistical procedures come up, and I should like to make the point that I do not attempt to draw any firm conclusions; I try to point out that there are these correlations but you are the people who are in a position to follow them up. With regard to the working mothers, surprisingly enough we did know about the baths for the housing schedule was remarkably complete. No doubt baths are a separate factor but, over and above, beside or between the baths, working seemed to have some influence. I admit that in another sample things might be different, but the whole point of this sort of work is to try and sort out relatively weak genetic and environmental influences, to provide a basis upon which the clinician can work.

PROFESSOR INGELMAN-SUNDBERG (Stockholm)

I THINK that intra-uterine asphyxia in itself is not as dangerous to the baby as the management after birth. The paediatrician may be as responsible for certain damage as the obstetrician and perhaps more, especially as some like to keep the prematures very warm, thus increasing their oxygen consumption. Based upon research on aborted foetuses studied in an artificial circulation unit, we have in my clinic in Stockholm developed a new method of resuscitation for deeply asphyxiated babies. Babies where the heart has stopped are given an intra-arterial transfusion of oxygenated blood, are cooled down to 25° C., and oxygen is administered into the stomach. We first used this method just one year ago; 6 apparently dead babies were treated after all other methods of resuscitation had failed. The babies have been carefully studied from a neurological point of view, especially concerning the hearing centre which has been tested with a special method covering frequencies from 300 to 3,000 cycles, and the hearing has been quite normal. One baby died on the second day of aspiration of vomit, the others have been completely normal to date (1 year).

I, therefore, think that there is some difference between the brain of the baby which is still *in utero* and the brain of the baby after birth. The foetus can tolerate lack of oxygen for some time but after birth we have to be very careful that the baby should have enough oxygen. If we cannot give sufficient oxygen, we should cool it down so that consumption is decreased.

MR. J. A. CHALMERS (Worcester)

As I listened to this discussion today it seemed to me that what I have to say may be relevant to some small part of our problem. I want to bring to your notice an apparatus which is being

widely used throughout most of Europe but not very much, so far as I can see, in this country nor in the United States of America. I refer to the vacuum extractor which I first saw in use in Brussels some years ago and which we have been using for some time in Worcester, very largely to replace forceps. Dr. Reid this morning has told us of the danger of forceps and also of the danger of anaesthesia in delivery, and I feel that both of these may contribute to some of the problems that we have been discussing.

The instrument which we have used is one with which many of you are no doubt familiar. The function of this device is merely to obtain adhesion to the foetal head to aid extraction and it can be applied in two separate ways. Malmstrom originally described it as used for prolonged traction on the foetal head during the first stage of labour when he generally applied a weight traction, but in his later paper he described its use for delivery where manual traction was used by means of the traction bar. In addition to actual descent of the head, it can achieve, or at least it can help to promote, dilatation of the incompletely dilated cervix; furthermore, it can obtain rotation of the mal-rotated head in a manner which is very close to the normal physiological pattern achieved by the pelvic floor. We have found that we can obtain powerful traction by means of this device, but if we try to employ it in cases where there is considerable cephalo-pelvic disproportion (we have indeed used it in much the same way as the "trial forceps" described by Professor Jeffcoate and others), it will detach itself. It produces a rather formidable caput; what happens is that the scalp is pulled up into and fills the cup. This artificial caput is rather terrifying when the child is at first delivered, but within about 20 minutes it is no more obvious than the normal caput. We have undertaken delivery of about 90 cases during the past 13 months and have been able to use the machine as a substitute for forceps in almost all cases. The exceptions are notably those in which there is acute foetal distress and those where there is a material degree of cephalo-pelvic disproportion. We have used it in premature children with satisfactory results and believe that it has certain advantages over forceps. In the first place it produces minimal foetal trauma, the compression of the foetal head being estimated as 1/20th that applied by forceps. Secondly, it does not encroach in any way on the birth canal, therefore there is less risk of the introduction of infection, it is applied to the lowest part of the foetal head and it can be applied with minimal anaesthesia; we have used pudendal block or episiotomy infiltration for almost all our cases. We believe that this technique can contribute materially to a reduction in neonatal asphyxia and therefore to the problems which we have been considering today.

DR. DUNCAN REID (Boston) (*Summing Up*)

I WANT to take this opportunity to thank the Committee for inviting me to participate in this Congress. The fact that there were no questions from the floor would indicate that the situation has reached a point which we refer to in the States: "No souls are saved after 10 o'clock at night", and my remarks will be very brief indeed. I should like simply to say again that we are confronted with basic problems concerning a better understanding of the reproductive process.

I should like just briefly to comment on Dr. Boyd's paper. We are also trying to treat the so-called incompetent internal os, and his simple method is to be recommended—we do about the same thing. The fact that the suture can be readily removed recommends it as a technique, for some of the suture material advocated is difficult to take out. When a failure occurs, in other words a patient bleeds or the membranes rupture, the question of infection arises; if the sutures can easily be removed, the pregnancy can terminate and the risk to the mother be reduced. The hazard of infection must not be minimized.

As regards Dr. Stewart's paper I should like to say that we have conducted a series where we tried to reduce the fat women. We have about 200 cases, and the pregnancies have been quite uneventful. These women have been dieted to the point of losing 30 or 40 pounds during the course of pregnancy, the babies have been born in good condition and the women have come

back post-partum having gained everything they lost!

I think Professor Walker has pointed out the main problem: what are the social and what are the genetic factors? Certainly nobody can deny the social aspects. We know, for example, that the incidence of prematurity in our institution (where few privileged patients are admitted) is somewhere in the neighbourhood of 18 per cent. Sir Dugald Baird did touch on the other side of the coin, namely, why are these babies arriving in such prodigious numbers in these families? Let us remember this important aspect—the control of world population and what it means in a democratic society.

Dr. Fraser gave us a tremendously interesting paper of a retrospective study, something we could all understand. He seems to lay stress on the respiratory aspects of these babies but, as we mentioned this morning, Dr. Apgar places more emphasis on the circulatory system. Dr. Jacobson, who is now away from our clinic working on subprimates, tells us that this applies to the subprimate as well. Once the heart rate drops to within the neighbourhood of 40 per minute, it is most difficult to resuscitate the newborn Rhesus monkey. In passing it might be of some interest and some assurance to us as humans that the subprimate cannot apparently stand anoxia to the degree with which the human foetus can deal.

In this country there have been some remarkable retrospective studies which have shed a good deal of light but we must realize that we need prospective studies. On this we will close: in the United States, as many of you are aware, we are now involved in a prospective study (in the National Institute of Health) of neurological diseases and blindness. It involves 15 institutions and both Dr. Taylor and myself have the privilege to participate. Valuable data will be collected by workers other than obstetricians to make the results as objective as possible. Perhaps somewhere along the line, in another 15 or 20 years, we shall be able truly to separate what is environmental from what is genetic.

STRESS AND THE FEMALE ROLE

BY

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PREAMBLE

IN this paper I propose to survey some of the effects of stress upon the functions and well-being of woman, bodily and mental. Since the field is a large one, a survey in this compass must perforce be of outline only—a kind of aerial view that allows the observer aloft to perceive, with more or less distinctness, the extent of the continent, so to say; its borders and subdivisions; the regions where it merges with other areas of biology—such as the social sciences; and the numerous zones of blank space on the map—a reminder that despite many years of patient endeavour, little or nothing is known about the nature, mechanism and meaning of several common disorders, such as period pain. I shall mention, also briefly, the personal and social patterns of behaviour which seem to contribute most to the arousal of stress in the patient; the causal agents not in the behavioural field, such as the influenza virus; and lastly, the methods of therapy that have proved most useful in disorders of women, in the out-patient clinic and the surgery of the family doctor.

The orientation of this outline may be called, for want of a better word, "psychosomatic". This word, introduced into medicine by one of our pioneers, Flanders Dunbar, has served a long and honourable term of office, and might now be granted an appropriate distinction, and allowed to retire. It was "minted" to convey the sense of a particular kind of approach to the patient—an approach that took account of her psyche as well as her soma: an approach, indeed, that all of us—if this were Utopia—should adopt to every patient all the time. However, it does in itself contain the very dichotomy—psyche-soma—we are striving to avoid. My own view, for what it is worth, is that a more fitting term for a comprehensive approach to medicine is "biological", or "human".

DEFINITIONS

The term "stress" may be defined as the internal or resisting force brought into being in the human organism by interaction with the environment (O'Neill, 1958a). In our culture, in the present day, one of the most important forms of such interaction, in the production of illness is that between man and his fellow-beings. The stresses arising from this source are manifested in disturbances of thought, feeling and behaviour, and in disturbances of bodily function. These may be brief and insignificant, or so persistent and troublesome as to constitute an illness; the group of illnesses in which stress is a principal factor in causation may be collectively called the stress disorders. Disturbance of function, if it is left untreated, may—and indeed often does—give place to structural change: what begins as bronchial spasm, in the anxious, over-protected child, can end with kyphosis, emphysema, heart failure and wrecking of a life. Menorrhagia of emotional origin can be so severe as to constitute a grave threat to the patient, and thus force the surgeon to a hysterectomy he is reluctant to carry out. Misuse of

the term "functional" has at times encouraged the presumption that the "disorders of adaptation" are of little consequence, and minor degree: to refute this, one need only look at the tally of stress disorders known to have been lethal.

A lucid and critical review of the present state of knowledge as to the place of stress in medicine is to be found in Chapter 6 of *The Nature of Stress Disorder*: it is the summing-up by John Wisdom (1959), a philosopher, of the papers and discussion at the conference convened in May, 1958, at the Royal College of Physicians, by the Society for Psychosomatic Research.

Scope of the Survey

At the periphery of the "continent" there lie a whole chain of regions that might be named "Territory of the Minor Discontents"—wherein disharmony in personal relations between one woman and another, or a woman and her man, provokes strife, unhappiness, envy, possessiveness, and other "disintegrative" emotional charges—troublesome enough, impairing creativeness and fulfilment, but not in themselves so distressing as to drive the patient to her family doctor and the surgeon. Farther inland, we have the zones corresponding to one or another of those disorders we see every day: here, the state of stress, within the patient, has "crystallized" into a bodily illness, or a mental disturbance, or—much the most common form—a blend of both. Nowadays, symptoms are much more often multiple than single, and illnesses more often complex than simple. The patient with a single symptom is quite unusual: of a consecutive series of 60 women attending an out-patient clinic studied by Norman Morris and myself in 1953–54, only seven complained of one symptom (Morris and O'Neill, 1958).

What is known of the incidence of "gynaecological stress disorder"? The answer to this question is quickly given: very little. The patients just mentioned were seen on one clinic day at the Obstetric Hospital, University College Hospital, over one year; a sample was drawn from the total number of women applying for an appointment; it was, I believe, a random sample, and can be taken to give a fair picture of "illness-scatter" among women in the metropolitan district and its environs. There have been few "random surveys" to draw upon for data; some others are the study by Finlay and his colleagues (1954), and the observations by Mestitz (1957) on attendance in a casualty department.

Some estimates are available to give an indication of the incidence of stress disorder, as one class, in the total volume of illness. The survey reported by Finlay *et al.* (1954) showed that, by and large, one-fifth of the patients seen on any one day in an urban practice suffer from a stress disorder. A similar survey, now nearing completion, of illness in the population of a large London industrial office, more recently, suggests that the proportion of stress disorder may be as high as 40 per cent. The second most common group of complaints among first attendances at surgery, in one division of Rolls-Royce Ltd.—some 20,000 men—was "headache and fatigue" (Levin, 1959): symptoms which are—if I may be so bold as to say this—seldom of "organic" origin, in ordinary medical practice.

The main conclusion of the Obstetric Hospital survey was that emotional tension outweighs physical malfunction and disease as a cause of illness in women who attend an out-patient clinic for gynaecology. This conclusion is, at first sight, rather startling, but it is the outcome of a long and close scrutiny of facts of clinical observation: given these facts, the conclusion is inescapable.

I—The Menstrual Cycle

That mood and feeling in women follow the cyclic variation of a universal biological rhythm is well known; in men, signs of a similar, though less well-defined, rhythm may be discerned, in the fluctuation of disorders such as urticaria. In the same way, menopausal "storms" in women are echoed by states of tension-depression at the menopausal epoch in men. For the clinician, the main importance of this rhythmic fluctuation of "pressure" in the female is that attacks of a stress disorder, such as vasomotor rhinitis, may be provoked by the general rise in tension-level during the premenstrual phase. The degree of discomfort, or disorganization, endured in this phase of the

cycle varies considerably from one woman to another, and in the same woman at different stages in the unfolding of her life: if she has other reasons for being tense—for instance, domestic discord—she will have more trouble at this time than if she were at ease and content. Physical methods of treatment, such as dehydration, I have found helpful in some women, provided always that the illness is kept in perspective against the patient's personality and mode of life.

Mood variations of this kind are, as a rule, within the limits of normal. A few women react more violently, and the morbid or excessive reactions may be listed as:

(1) *Menstrual Psychosis*

The patient is, for a few days, before or around the period, so disturbed as to be insane. Two forms of this illness I have encountered are (*a*) the paranoid—with delusions of persecution, and (*b*) the depressive—with delusions of bodily disorder, and self-accusatory feelings; no doubt there are various other forms of it as well.

My impression is that this disorder is a rarity; although I look out for such cases, I have not been able to collect more than a few. One salient feature of menstrual psychosis is the transience of each attack—although if the emotional disequilibrium which "feeds" the illness is not dealt with, the next period will excite another attack.

The "preparation for illness" in women with this disorder is dominated by frustration of one or more of the chief biological functions of women, such as sexual enjoyment or motherhood.

(2) *Over-reaction to the Period*

Here the clinical picture is made up of exaggerations or distortions of the normal "menstrual syndrome", and a variety of other symptoms—such as panic attacks, depressive waves or hypochondria—which are a reaction to these.

(3) *The Atalanta Reaction*

Menstruation is a recurrent reminder of female-ness, and hence the woman's attitude towards it is a reflection of her attitude towards the role which social custom obliges her to play—acceptance, or rejection, or any mixture of the two.

The symptom-cluster to which I have given the title "Atalanta syndrome" is: period pain, irregularity, frigidity, dyspareunia, abortion or miscarriage, vomiting in pregnancy after the 3rd month, undue difficulty and distress in labour, depressive spells of unusual intensity after the birth, failure of lactation, menorrhagia and amenorrhoea. Among normal women attending for antenatal or postnatal care, the mean number of symptoms per patient was 1·6; women with stress disorders tend to have more than this—in a comparable group of female patients, the mean was 4·6 (O'Neill, 1951). In women whose "male identification" is strong, the count may reach 10 or 11.

The "Atalanta count" has some predictive value, in that it may be possible to forecast, say, that labour will be unusually prolonged, or unpleasant, or complicated in some way.

In female patients who attend regularly and over a long time, the physician may come to have such intimate and detailed knowledge of the relation between stress and the menstrual cycle that no variation from the normal pattern remains inexplicable—indeed, in women undergoing therapy for several years, the only hypothesis accounting for the observed reactions is that the character of the cycle, in each of its aspects, is governed by the patient's life-situation and the stress it provokes. Intensive study of even a few patients "in depth" is, in my view, essential for the understanding of any disorder—it adds another dimension to the clinical experience of clinic or surgery, where patients are of necessity seen briefly and at longer intervals. The menstrual cycle, in most women, is very sensitive to changes in emotional balance—the ebb and flow of feeling is mirrored, day by day and even hour by hour, by variations in period pain, or quantity, or timing.

Of course, there are many "open questions"—why does one woman react to adversity by excessive bleeding, while in another the periods vanish for months on end? This question—of "choice of illness"—has been debated, and argued over, for one or two decades in Europe and America, but no satisfactory answer has

emerged. Three possible "determinants of choice" are suggested in the paper mentioned above (O'Neill, 1958a). The four common stress disorders of the menstrual cycle—menorrhagia, irregularity, period pain and amenorrhoea—are now so familiar that no more need be said about them. In this country, in the year 1959, the principal pathogenic agent for all four is in the emotional field: a state of frustration or tension that the patient cannot resolve by action, speech or thought. Menorrhagia which is not too heavily "charged" may clear up after dilatation and curettage: this is not a proof that the bleeding was of physical origin—it shows only that the "impact" of the surgeon (including his procedures) on the patient had some therapeutic value; only continued supervision of that patient over, say, five years will allow an appraisal of how much value it had. The experienced surgeon will often admit that the "personal equation" counts for more than any medical or surgical remedy—the most important drug in medicine today, in fact, is the doctor himself (Balint, 1957).

Of these four disorders, amenorrhoea and excessive bleeding are the more readily understood: their determinants, in the "life within and the life without", are near the surface, and patients do well with the kind of therapy which out-patient staff or family doctors can themselves carry out. One method I have used and recommended for some years is that of controlled stimulation of "emotional release" (O'Neill, 1959a); the hazards are few, and the benefits many—both for the patient and her medical attendant: an interview assisted by Methedrine may enlarge the insight in both parties, and add to the doctor's therapeutic effectiveness, not merely in that patient but others as well. The aphorism that patients are the best teachers of medicine has more than a grain of truth in it.

Irregularity in the cycle is so prevalent that it can scarcely be called a "symptom": it is seldom brought to the clinic as a presenting complaint, unless a subsequent fear of pregnancy, or some other attendant symptom, has grown up around it. It merits no especial remedial attention, and will generally clear up when the antecedent tension state dies down.

Pain at the period is another matter. Just as the biochemical substratum and the neurophysiology of normal menstruation is but partially understood, so the physical basis, the nature and purpose, of this everyday disorder is, for the most part, guess-work. The pain, in some women, meets all three criteria of a stress disorder; at the "top end" of the Atalanta scale, a woman's reaction at period time is what one would expect it to be. There is a class of young women whose pain is quite simply the product of ignorance, superstition and fear: they come to the menarche unprepared, or made illness-prone by a mother who is herself in trouble: these girls profit from therapy, unless crippled by poor intellect or gross timidity. Beyond these is the class of women with pain at the period that defies all therapy and every doctor; here, I think, one must in honesty admit defeat. It is too easy, and too facile, to accuse the patient of "wanting the pain"—the plain truth is that the nature and pathogenesis of illness in these women are obscure, so that treatment directed at the causes of suffering cannot be applied. It is fair to say, however, that the number of patients falling into this class is not great.

II—Reproduction

(1) *Conception*

The capacity to conceive may be blocked altogether, or impeded, or delayed, in a woman without bodily disease, by emotional tension. Here is a stress response which commands less general acceptance than it should. The mechanism of this kind of infertility is in doubt: tubal spasm has been suggested, and certainly in some women it can be demonstrated in direct relation to emotional state. For myself, the most convincing proof of emotional blocking of conception comes from the work of Bernard Sandler (1959), who looks after an Infertility Clinic in Manchester. Dr. Sandler reckons that one-quarter of the women he sees fail to conceive because of some concomitant failure of adaptation to the people and conditions of their "world". His case records, I think, speak for themselves—they are better evidence than a thousand pages of theoretical dissertation. I recall most vividly

his account of one woman whose tubes, on screening, were quite occluded—until he contrived to make her laugh: with the tension-relief of laughter, they relaxed, and later she conceived without further therapy. It goes without saying that the natural biological drive, in the majority of women, is towards conception: left to itself, the reproductive process will function efficiently, with only that degree of failure or "wastage" that goes with the "graph of normal distribution". If we can agree with Dr. Sandler, stress is the second commonest cause of persistent blocking of conception: once the doctor is aware of its existence, he can help the patient much more, and thus be relieved of his own frustration.

I have not space here to dwell on the concept of the "endocrine tranquillizer" that appears to operate in so many pregnant women during the second trimester (Morris, 1959). The patient will say—"I feel better now than I ever did in my life". Whatever its nature, it is capable of damping down anxiety, and "neutralizing" tension symptoms. Its action begins to dwindle as the time of birth draws near; after the baby is born, the mother may feel an intense sense of "let-down", and this rebound effect is, I believe, an important cause of breakdown in the post-partum phase. This endocrine or biochemical euphoria has not yet made its entrance in the first trimester: some fatigue or languor, or nausea, or other signs of "re-adjustment", must be regarded as normal—at any rate in our society. If the nausea passes over into vomiting, and especially if vomiting continues after three months, then the limits of normal have been exceeded and the woman is no longer discomforted but ill. Tension signs in the second three months have particular significance, for they point to an internal pressure high enough to overthrow the natural "stabilizer".

The normal sequence of events at parturition can be disrupted or disorganized in a variety of ways if the patient enters upon it in a state of stress. Unusual difficulty or distress is one such way: unusual delay in delivery is another. The incidence of "bad labours" is above average in women who have suffered an earlier "breakdown" (Tylden, 1959), and in those with high "Atalanta count" and an active rivalry with the male. Hypnosis as a means of easing labour has been tried out by Stanley Perchard (1955); it seems to be beyond dispute that women in the hypnotic state have a more pleasant, or less unpleasant, time in the course of labour, and are much more prone to forget the unpleasantness completely. Perchard makes only modest claims for his method; it would be true, I think, to say, that the occurrence of "complications" is about the same in women taken through labour under hypnosis as in any other comparable group, though the subjective experience is more pleasant.

After delivery in hospital, two women out of three pass through a brief spell of depression: it is generally brief, reaches its peak in the 3rd, 4th or 5th day, and quickly subsides. A minority suffer more severely, and some of these turn out to have been avid disciples of "relaxation": the reason seems to be that they expected a mystical or ecstatic experience, and instead were obliged to tolerate the ordinary pains of delivery. Thus, they feel disappointed, chagrined, and let-down, and in consequence resentful and depressed. Among the rest, a "reason" is always found for the depressive spell: the baby will not feed, he is sick in some way, or separated from the mother; "Grandmother came to call", and the like. The observer is inclined to call this "reason" a rationalization: the mood disorder came first—perhaps a result of withdrawal of the "endocrine sedative"—and then a cause must be found for it.

Conception out of wedlock is a curious and intriguing "disorder", and it poses a formidable problem to the community. Some four to five hundred of these girls are seen at Queen Charlotte's every year, and my colleague Miss Celia Jones, the Head Almoner, has embarked on a study of the antecedents and conditions of unwanted birth, and the kind of girl who is prone to it. Our impression is that only seldom is such a conception a chance event—in the great majority, the pregnancy is motivated, whether its purpose lies inside the "perimeter" of conscious awareness or not. The girl's state of mind at the time of conception does very often show a sort of "splitting"—she knows that coitus without protection may end in conception, she does not "want" the baby—

but it happens. So, then, conceptions in this type belong to the class of parapraxias—events that appear accidental but are not: a class which includes "accidents" at work—the employee whose finger gets caught in a machine he has been working with for ten years—the difference being only that the "accidental" pregnancy is directed less at the girl herself than at the people in her "world", especially the mother, while the machine-injury is more self-destructive and less of a revenge on the employer. In those girls I have seen, separation from the mother, or emotional deprivation, has been plainly evident in the life-story; the girl, at interview, is remarkably casual and indifferent —she seems to have little feeling for the baby, or its father, or its welfare—"Mum will take care of that" she says blandly. Her attitude is, in effect, that her parents are responsible for the whole thing, and must therefore "carry the can".

(2) *Delivery*

If the process of parturition is placed alongside the other female functions, and the effect of stress upon these reviewed, the inference is plain: it would indeed be strange if delivery were *not* subject to interference by stress and tension. If one were to single out a cardinal element in the causal complex of difficulty and delay in labour of emotional origin, it would be the attitude of rejection of the child, and perhaps, in more general terms, repudiation of the feminine role. If this be accepted, it follows that the incidence of "labour-disorders" will not be constant, but will vary with the prevailing concept of the female role. For instance, it might be argued that we are witnessing in Britain just now some degree of exchange of functions between the sexes: many more women are going out to work, and taking up careers that in former times were the preserve of the male; if they marry and bear children, their loyalties are at once divided—they are drawn one way by the lure of vocation (especially if it is a creative one), and the other way by motherhood and family life. There is room here for a controlled field study of the current "fashions" in what women should do and be, in parallel with the prevalence and nature of "labour disorders".

(3) *Mothering*

On the question of education for motherhood, the extremes are: (*a*) None at all: the expectant mother is presumed to be able to meet her tasks "by instinct"; imitation of, or identification with, her own mother; or gossip and old wives' tales; (*b*) Over-education—to the point where the hapless woman is rendered hesitant and hypochondriacal by the flood of pamphlets, broadcasts, textbooks, and advice by all manner of self-appointed authorities: so that in the end she scarcely dare give her baby his bottle without consulting a physician. A welcome antidote to this undue emphasis on the technicalities of child-care is Winnicott's admirable monograph (1956).

In the long view, the most important feature of disturbance of mothering-capacity is that it is self-perpetuating—the problem-mother produces a problem-daughter, who in turn may (if she is not given help at the right time) produce another of her kind. Perhaps the truth is that each generation makes its own problems: well-meaning "education", of itself, is by no means a panacea.

The "Causal Complex" in Disorders of Women

The notion of a "single cause" for any illness has now been abandoned: every disorder has several, perhaps many, determinants—a "causal complex". If he is to keep his feet on the ground, the doctor must recall that an illness with symptoms mainly in the physical sphere may have emotional tension as its principal determinant, and that, conversely, an illness that appears purely "psychiatric" may be the end-result of organic disease, such as cerebral tumour.

Depression "colours" many of the illnesses seen in a women's clinic; depression and tension pain (see below) are close together—of a series of 50 patients with tension pain, 29 gave depression as one of their complaints, and four of these were ill enough to require electroplexy (O'Neill, 1958b). As a causal agent of depression over the last few years, the influenza viruses must take one of the top places. In the

epidemic of 1957 it was estimated that some eight million people fell victim to one or another of the viruses; if only one in four suffered the post-viral state (O'Neill, 1959b), then two million cases of depression in the spring of that year may be ascribed, more or less directly, to virus infection.

Several other types of causal agent might be mentioned, but the post-viral state does, I think, overshadow the rest just now by reason of its high incidence and disruptive effects.

Final Comment On the Significance of Pain in Gynaecological Practice

One finding of the University College Hospital survey, which came as something of a surprise, was that pain was "well out in front" as a presenting symptom in the out-patient clinic. More than one-third of the series gave pain (apart from period pain) as a leading symptom; of the remainder, about one-third described pain as one part of their complaint. Thus, in round figures, two women out of every three attending the clinic reported bodily pain as a major or a minor symptom, or pain at the period.

Where pain was the presenting symptom, we took especial care to satisfy ourselves that every possible organic cause for the painful sensations was canvassed, but even so we could find no more than three cases in which the sensations, as described by the patient, were fully accounted for by a physical disorder. In all the rest, the presumptive diagnosis was tension pain. Many of these women had pain of the same quality, site, and time relations as one may find in patients attending a Department of Physical Medicine: but tension pain is not a "rheumatic" disorder, nor a "gynaecological" one—it is a stress disorder, and behaves accordingly. However, it is an exception to the general rule that most of the illnesses in this category do well under treatment. The results of therapy of tension pain are disappointing, and often the only result is frustration in the doctor. Comparing the clinical picture of tension pain in women—most of the patients *are* women: the ratio of female to male is in the region of 10 to 1—as it appears in general practice and in the various hospital out-patient departments, one cannot help wondering whether the department of referral (I imagine the majority of them are sent, sooner or later, to a clinic) is determined by the site of the pain more than anything else. So, when pain is felt across the lower abdomen or back, the patient is sent to the Department of Gynaecology—not because she has any illness within the surgeon's province, but she has pain in the "gynaecological area".

It is fair to say that the sequence *stress→tension→pain* occurs more often in the disorders of women than anywhere else in the entire spectrum of human illness. The reason for this has still to be determined: perhaps one clue lies in Helene Deutsch's (1947) doctrine that masochism is one of the three essential traits of femininity.

Summary

An outline is given of the relation of stress and emotional tension to some of the functions proper to the female role, and some clinical observations are provided to illustrate the principles set out.

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DISCUSSION ON PSYCHOSOMATIC GYNAECOLOGY

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DURING the latter part of the nineteenth century men's thoughts and speculation were awakened and dominated by the work of a brilliant galaxy of natural scientists; some of whom were Darwin, A. R. Wallace, T. H. Huxley, Lyell the geologist, Tyndall the botanist, Helmholtz and J. J. Thompson, the physicists, and many others. Against this materialist biological and physical background, medicine enjoyed a similar evolution by the discoveries of Pasteur, Metchnikoff, Virchow, Koch, Lister and J. Y. Simpson.

The work of all these pioneers focussed men's minds on the material elements in life to the exclusion of any recognition of the influence of the emotions on the physical functions. The fanatic opposition of the Church to the theory of the origin of the species was matched by Huxley's provocative dictum that "the brain secretes thought as the liver secretes bile".

The influence of the materialist view of our physical functions was profound. A purely mechanical idea of the causes of physical symptoms of illness persisted well into this century. The scope of surgery was rapidly expanding by an increasing technical skill which enabled hitherto unknown recesses of the body to be safely explored. All symptoms of which a patient complained must have an organic cause for which more and more ingenious operations were devised. Chief amongst these were the "fixation" operations by which the stomach could be pleated for flatulent dilatation or the kidneys stitched up for backache even if they had only their normal mobility; the caecum was pleated for chronic pain in the right side (after the probably normal appendix had been removed) and a retroverted uterus was suspended or fixed forward for almost every gynaecological symptom. But while this riot of futile surgery was flourishing in all our hospitals and especially in the private nursing homes, there was a great psychologist, Freud, at work in Vienna beginning to explore the deeps of the human mind. Others were Jung and Adler.

It was not until after the first world war that surgeons became aware of the failure of the fixation operations, which, consequently, were gradually discarded. With the intense study and rapid progress of bacteriology the new idea which possessed the profession was the concept of "focal sepsis" as the hitherto unrecognized cause of a multitude of diseases. This began in the early 1900's and persisted for 20 years. It led to wholesale dental extractions, tonsillectomy, appendicectomy and even, in the hands of a few fanatics, complete colectomy for arthritis and "chronic mastitis"—the condition we now call "fibro-adenosis" and which is not an inflammatory disease. Endocrinology became an increasing sphere of medicine in the 1920's and is still progressing. It first led to a recognition of the possibility of symptoms being due to disturbance of visceral function, an idea which was supported by the frequent negative X-ray examinations of the alimentary tract for gastric and intestinal complaints. Despite clinical diagnosis of organic lesions, time after time these were found by X-ray to be non-existent.

Meanwhile the psychologists were hammering away at the enormous importance of fear, anxiety and other malign emotions in disturbing function in the absence of organic disease. Perhaps the pendulum is swinging too far in this direction inasmuch as an easy diagnosis of a functional upset may excuse a careful search for the beginnings of a true organic lesion.

THE EMOTIONS

Our emotions or feelings are part of ourselves in varying kind and degree all the day long, usually so mild as scarcely to be noticed but occasionally so violent as to interfere with physical health. There are two inborn emotions which determine patterns of behaviour under specific conditions. They are not acquired by experience or derived from individual contacts in ordinary social life. They are *pure* emotions inasmuch as they are instincts which cannot be divided.

The first is that of *self-preservation* which evokes *fear* for the self or the young of the mother animal, and leads to fight or flight. All the endocrine functions are mobilized, it may be in a matter of moments, to tense the muscles for overcoming the source of the fear. Among the secondary effects of the endocrine and autonomic nervous reaction are the dry mouth, sweating, dilated pupils, trembling, rapid heart beat and respiration and general tension of the whole body.

Here is a disturbance of function caused by a primary instinct, fear. But fear may be an almost constant state of mind in some people, or be aroused by causes far short of self-preservation. Ordinary civilized life presents a multitude of trivial incidents including minor transient pains which, in some individuals, provoke uncontrolled and unreasonable fear with its inevitable physical reactions. These gradually build up into a pattern of symptoms we call a neurosis. The majority, however, of both sexes are able to control the reactions to fear either by an innate toughness which derives from the power of logical reasoning on the relative harmlessness of the fear-provoking incident, or as a result of training, guidance, experience and discipline. The obvious example of the latter is the soldier who at the beginning of his service may be and usually is frightened, often terrified by the risk and noise of battle, but this primary emotion of fear soon becomes controlled by repeated experience and the discipline of training. There are some, however, who never acquire control through any amount of experience and training and remain in the grip of fear all their lives.

As a gynaecologist one commonly sees women patients who seem to nurse fears of all kinds. They are impervious to the appeal of reason and entirely uninfluenced by attempts to reassure them. Examples are the fear of cancer, of pregnancy when menstruation naturally ceases at the menopausal age, or, after even a short time of marriage, of remaining childless. No amount of reassurance after careful examination will convince them that they have no growths, that pregnancy is nigh impossible at the menopause, or that very many women become pregnant after longer than, say, 3 years of marriage.

The second primary instinct is that of *reproduction* which responds to sexual stimuli, chiefly by the senses of sight and smell in mammals and birds. Man differs from the mammals in possessing minimal stimulus from smell; it is replaced by the much greater influence of sight and also of touch. In clinical work we find neuroses developing chiefly from a defect of the sexual instinct in both men and women, and also, in a few women, from an excessive desire which remains ungratified. Sexual frigidity in a young married woman usually causes an anxiety neurosis and may end in a decree of nullity which adds a further severe stress. But just as fear, anxiety and unhappiness can depress health, so the joyful emotions can and do exalt it by maintaining an efficient and co-ordinated functional system of the whole body. It is common knowledge that a happy individual is free from the neuroses which afflict the victim of anxiety. The experience of a deep and satisfied love makes for the greatest of all happiness. How perfectly Shakespeare describes this in *Love's Labour's Lost*:

> "But love, first learned in a lady's eyes,
> Lives not alone immured in the brain;
> But with the motion of all elements,
> Courses as swift as thought in every power,
> And gives to every power a double power,
> Above their functions and their offices."

Here is the poet's word-picture of the exuberance of health which comes to us when we are extremely happy.

The Stresses

The external stresses of modern civilized life will produce varying degrees of anxiety depending upon the nature and strength of the stress and the toughness of the individual's resistance. Two people will react differently to a similar stress in their emotion of anxiety or fear and consequently in their later liability to a neurosis. The weak personality will succumb quickly but the intelligent well-controlled and disciplined mind will probably remain free of neurotic symptoms. For women the usual stresses are interpersonal relationships which are as a rule deeply derived from the paramount importance of the role played by the sexual organs and their functions. Examples of common stresses to which women are subjects are:

(1) The mental unrest of puberty and early adolescence. The child becomes a physiological woman by a rapid development of her pelvis, uterus, ovaries, breasts and physical contours, which is largely completed within 18 months. In addition her mind suddenly ceases to be that of a child inasmuch as she becomes conscious of her sex as something fundamentally different from that of the male. In other words she has eaten the apple of Eden. It is not surprising, therefore, that girls passing through the years of puberty and early adolescence often suffer from mental conflicts. The new experience of emancipation from the constraints of childhood and consequent uncertainties of behaviour, especially in her new relations with young men, cause resentment of continued parental control and vagaries of temper. Further, it is during these years that the child is expected to face responsibility in the shape of examinations at school, higher education or work in her first job. Thus the girl may suffer from a sense of inadequacy, conflict, fear and the anxiety which follows fear. Sometimes these malign emotions react on her physical functions; the chief manifestations are menstrual disorder, fatigue, restlessness and insomnia, a group now known as psychosomatic illness.

(2) Sexual disharmony of young married couples is not uncommon. It may be caused by or lead to sexual frigidity which is often incurable and thereby destructive of married happiness. As Sir Alan Herbert writes in *Holy Deadlock*: "If the bedroom's not right, then every room in the house is wrong." Other causes of disharmony are frustration of normal desire or exhaustion due to excessive libido of either partner. Sooner or later these evil conditions will exert their influence on a woman's physical functions and she will become a psychosomatic patient.

(3) The great majority of all married women want and expect a family, very few being content to marry for no more than security and companionship. Failure to conceive or the loss of a child by miscarriage or stillbirth is a serious matter for most women but for some it is a tragedy which devastates their lives. For these unfortunates the continuing privation of children causes deep and unrelieved depression. They pass from one specialist to another in the vain hope that some new and successful treatment will be found. Here again is an obsessive fear. The probable result is the development of some form of psychosomatic illness.

(4) The opposite state, that of repeated and unwanted pregnancies, is liable to impair physical vitality not only by too frequent childbearing, but perhaps even more by a hopeless fear that every sexual act will result in yet another pregnancy. Normal marital life loses its interest and even becomes repugnant to the grand multipara because of its possible consequence. These women are tired, lifeless and worn out. The state of constant fear, depression and fatigue will inevitably exact its price in the form of physical symptoms.

(5) The menopause, or more accurately the climacteric, is physiologically the opposite to the changes which develop at puberty. Now the endocrine system of glands which have governed the reproductive years are involuting. The ovaries gradually and irregularly cease their production of oestrogen and progesterone over a variable period of years leaving the secretion of the pituitary gonadotrophins unchecked. It is believed that this is the chief cause of the paroxysmal vascular instability which shows itself by the characteristic hot flushes and sweats. While most women suffer only minor disability at the change of life, some are terribly distressed by depression, irritability, forgetfulness, failure of mental concentration, exhaustion and insomnia. In addition there are some somatic symptoms such as gain in weight, flatulence and distension, pruritus, skin lesions, loss of physical strength and growth of abnormal hair. Apart from these disabilities many women are troubled by their loss of youth which no longer can be disguised. They naturally feel that they have lost their attractiveness in social life, which, deep down, is one of the most precious of all

a woman's possessions. Also the libido may be failing (though sometimes the reverse happens) as the binding cement of married life, raising the ugly fear that perhaps an unsatisfied husband may lift his eyes to others. Loneliness is often an increasing feature of the menopausal age as the children are growing up and leaving home, while perhaps the husband's increasing responsibilities absorb more and more of the time which he used to spend at home. Many women now know that the menopause is the age of cancer which adds yet another fear to their troubled minds. It is not surprising, therefore, that psychosomatic illnesses are common during the stage of endocrine involution.

Psychosomatic Illness

I have repeatedly used the term—let me now try to define it. The word is derived from "psyche" the mind or spirit and "soma" the body. Whether what we regard as the "mind" is an entity separate from the body or is no more than an expression of cerebral activity and function cannot be discussed here and, in any case, I am not a competent exponent. As a working hypothesis let us assume that the mind and its emotions enjoy some form of separation from the soma, and yet the association of their activities with the consequent interplay of one on the other is so intimate that they are, so to speak, married into the unity of an individual personality.

The manifest expression of this relationship is the very frequent co-existence of symptoms of all kinds with states of fear and anxiety in the absence of any discoverable organic pathology. I should add, however, that some early lesions may be impossible to recognize however careful the examination (short of operation). Well known examples are pelvic tuberculosis and certain ovarian causes of sterility. Nevertheless there are features of psychosomatic illness which differentiate it clearly from organic disease.

This form of illness is essentially a disturbance of function of the various organs of the body, especially the endocrine glands. An example is the increased acid secretion and gastric spasm which is often induced by continued anxiety and mental tension, especially in men. Another is the menstrual disorder, either excess or suppression, caused by shock, fear and distress. If the patients are examined during the early stages of both these complaints, no peptic ulcer or uterine disease will be found. If the disturbance of function is continued over a long period, then sooner or later a true organic lesion such as a peptic ulcer will develop. The sequence, therefore, is anxiety and tension—disturbed function—organic disease.

For many years the existence of psychosomatic illness was denied by the majority of clinical workers and even now there are a few who claim that symptoms of any kind must be caused by a lesion which will be found if the search is sufficiently thorough. But there is much evidence that symptoms can be suffered in the absence of any lesion.

(1) Many complaints are cured by non-specific and useless drugs or by change of doctor to one who can impart confidence and hope. When we hear the common "I have a lot of faith in Dr. So-and-so", it is almost certain that this patient's symptoms will be much improved or abolished however useless his drugs may be. If anxiety and tension can be controlled by sedative drugs and sound advice, the patient will often be cured so long as his symptoms are due to disordered function and not to organic disease.

(2) The close relation of a severe and continued stress causing fear and anxiety with the onset of symptoms in almost any part of the body and their disappearance when the stress is lifted is further strong evidence of an illness or disability being caused only by some form of dysfunction.

(3) Certain personalities are prone to suffer from the same groups of symptoms. The ambitious, hardworking, precise, exact (and exacting) type is especially liable to migraine. The occurrence of any anxiety or worry during the course of their daily lives may act as a trigger for firing off the attack of headache. Dysmenorrhoea is another example of a type-linked complaint. Some psychologists would have us believe that it expresses a

young woman's unconscious desire to repudiate her female sex. This is hard to accept when we remember that the worst form of incapacitating menstrual pain can be completely stopped at any given month by suppressing ovulation with a large dose of oestrogen. Dysmenorrhoea is much less common in factory workers than among skilled, responsible and sensitive young women. The girl is often an only daughter whose mother by her ill-advised teaching has passed her own dysmenorrhoea on to her daughter. A sense of frustration, inadequacy and failure (often buried beneath the surface of daily consciousness), due to social timidity and failure to be attractive to young men also forms a background. These people are unwilling to give up their dependence on their parents or others with whom they have been closely associated. They are timid, easily frightened by trivial occasions and want love with its protection. Such a woman may cease her periods for months after a bereavement or for no more reason than changing her work in a new environment.

(4) A fourth clinical type of psychosomatic disorder is the dyspareunia and sexual frigidity of the mother-fixed daughter for the husband can never compete with the possessive mother for his wife's interest, love and companionship. It is not surprising that these women reject the sexual act by frigidity and dyspareunia.

(5) Psychosomatic illness is never more obvious than in the polysymptomatic group, chiefly women. A feature of these people is the multiplicity of their symptoms. Their reply to every question is qualified by such words as "terrible", "awful", "agony" and other extremes of description. They admit headaches (usually "terrible"), backache, flatulent dyspepsia, "loss of the use of my legs", swelling of the ankles, "never a wink of sleep", nausea in the mornings, irregular periods and, invariably, "always tired". There is no conceivable organic pathology which can explain the polysymptomatic syndrome. These people are nearly always discontented with their lot in life, often fat and lazy, grumbling, sour and jealous. From other doctors and specialists they often arrive at the gynaecologist's consulting room with various menstrual disorders or backache. In my experience these women are the most incurable of all the psychosomatic group. Even if any one symptom can be relieved there will assuredly be an outbreak of another in some part of the body. Their complaints are marshalled to evoke interest in a feeble personality and to stimulate sympathy.

Gynaecological Symptoms Caused by Shock and Stress

As I have already said, *amenorrhoea* may follow not only shock but such apparently minor events as change of residence and work. The interesting features of these patients (which I wish to emphasize) are that the periods suddenly stop at the time of the stress and as suddenly reappear, usually in the absence of any treatment. Nothing abnormal can be discovered by examination under an anaesthetic but biopsy of the endometrium and the basal morning temperature chart generally, but not always, show an absence of ovulation. Further, there is no failure of subsequent fertility.

Menorrhagia is also a good example of a pelvic disorder resulting from shock, but in the opposite direction. During the early weeks of the War, when men were leaving home to join the forces with an unknown future before them, many of their wives used to come to out-patient clinics complaining of monthly excess or floodings (as commonly as those whose periods ceased). Another example is that of the wife who suffers the shock and distress of desertion by her husband or who has secret fears of his infidelity. Menorrhagia may last for months but sooner or later it disappears and the periods gradually become normal again.

Intractable *pruritus vulvae* may follow sexual privation. An outstanding example was a patient whose boy friend, a window cleaner, was killed by falling off a window sill. She was deeply distressed and came to me complaining of intolerable itching which destroyed her sleep.

No ordinary local applications had any effect whatever, nor had injection of the internal pudic nerves by a long-lasting local anaesthetic. Finally the woman was admitted to hospital for division of these nerves; again, no improvement. But, in a little time, she found another male companion and the itching ceased as suddenly as it had begun.

Another not uncommon complaint is an excessive *leucorrhoea* of clear cervical mucus. Thin and translucent with no trace of infection, it happens in adolescents at times of fatigue and depressed vitality or, in others, immediately after marriage. The secretion of mucus by the cervical glands is under the influence of ovarian oestrogen. Evidence of this is the abnormal secretion of the cervix in a post-menopausal woman who has taken large doses of stilboestrol or oestradiol for no more than three or four weeks. The inference is, therefore, that those young people who are troubled by an excess which is most inconvenient have some disturbance of the endocrine system whereby there is an abnormal and unchecked secretion of oestrogen.

There is also evidence that *infertility* is a psychosomatic phenomenon in those who are obsessively anxious to have children. If this is true it is due to the suppression of ovulation through a chain of endocrine events originating in the hypothalamus and acting through the anterior pituitary. We all know how often at the end of unsuccessful treatment conception quickly follows the adoption of a baby. In the absence of any physical abnormality of either partner, the satisfaction and new interest of adoption may, and probably does, release the inhibition of ovulation.

I have confined myself to the development of gynaecological symptoms, which are liable to follow the impact of fear, anxiety and unhappiness. But whether we are men or women the nemesis of fear will exact its penalty in the shape of some form of disordered health long before a true disease begins. The useless tragedy of fear is that most of it is baseless inasmuch as the spectre we are afraid of never materializes.

Some of you may remember the story of Christian's family in *Pilgrim's Progress* when they were led by Greatheart. They were terrified when they saw ahead of them a giant called Grim and a lion on either side of their track. Trembling with fear of the danger in front, they faltered behind Greatheart. But armed with strength and a trusty sword he slew the giant and showed the frightened family that the lions were chained.

And so most of the fears and anxieties which plague our lives with distress and ill-health are as groundless as those of the Christians in *Pilgrim's Progress*. I admit that it may be very difficult at times to discount anxiety which threatens us but even if it is real remember that Greatheart defeated the menacing giant with his strength, not only physical but of heart and mind. How much more, therefore, should we be impervious to the unsubstantial fears which we conjure up in our own minds! May I conclude by some words of Shakespeare:

> "Cowards die many times before their deaths;
> The valiant never taste of death but once."

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PSYCHOGENIC AMENORRHOEA

> "Because of the essential unity of the two things that we divide into somatic and psychic, one may prophesy that the day will come when the avenue from biology and chemistry to the phenomena of neurosis will be open for our understanding and we hope also for therapy" (Freud).

THE PSYCHOSOMATIC APPROACH

GYNAECOLOGISTS are apt to regard material dealing with abstract and subjective phenomena as the Cinderella of the specialty although every disease is a mixture of psychic and somatic factors. In private practice only about one-third of cases will prove to be organic: a tumour, displacement, infection, malformation, or aberration of conception. One-third are mainly functional, resulting from the interplay of psychodynamic forces, and the remaining third are a more even mixture of both, perhaps a fibroid and a fright.

Psyche and soma are not separable entities but merely different facets of the total entity, the

undivided or individual. Studies by tradition commence on the unicellular organisms, tissues and organs are arranged from histological patterns, and finally the body is assembled. In the spirit of Virchow causes are sought in the cellular pathology, and excuses are made for the limits of the microscope. Conversely it is easy to assume that when nothing is demonstrable there is no disease. The result is to produce the fallacy of thinking that the whole is the summation of its parts, whereas the reverse is true in that from a study of its parts the whole can neither be understood nor properly described. Symptoms which are real can be manufactured from subjective feelings, and structural changes may follow in the organs.

The close association of the functional complaints with gynaecology is shown by the word "hysterical", implying a wandering of the uterus. The Ancients showed some measure of insight when they visualized, say, a lump stuck in the gullet as being the corpus uteri itself. It is a quick and spectacular procedure to stop menstruation by hysterectomy, but it requires greater skill and time to cure cases of amenorrhoea when the uterus is present, although it can give much satisfaction.

Neuro-Endocrine Mechanisms

Local Vascular Changes: The thick secretory endometrial bed is nourished by a specially developed vascular system consisting of a number of coiled arterioles which support the superficial compact layer. These arterioles were considered to be endarteries opening distally into venous pools, but it has been shown also that there are proximal anastomoses with corresponding venules which normally are closed but can open under nervous and chemical control. Opening of the proximal shunt diverts blood from the surface producing an ischaemic necrosis, and fills the venous pools at arterial pressure. This spasm and shunt is responsible for bleeding and for the "blush and blanch" effect.

Hormonic Control: Hormones are responsible for endometrial structure, but the bleeding is mediated by vascular gymnastics, particularly when hormonic support is withdrawn, and it can break through from any type of endometrium, secretory, proliferative, hyperplastic, resting, or atrophic. Apart from this primitive slow-acting chemical system, nervous influences may act quickly and independently on the flow.

Nervous Influences: The primary pace-maker of the cycle resides in the hypothalamus. Centres in this region are influenced by light waves from the retina, which exert a seasonal control on ovulation in animals and birds, and are concerned in coital-induced ovulation in some species. Everett and Sawyer (1949) have shown that there are pulsating waves in the hypothalamic-hypophyseal pathway along the stalk, which in some animals have a diurnal variation, or phase-sequence, which can be timed to certain hours of the clock. The nerve centres in the hypothalamus can be selectively affected and the rhythm disturbed by the action of various drugs, as demonstrated by Barraclough and Sawyer (1957), and Velardo (1958).

Superimposed on the control through the hormonic chain is the autonomic nervous system which has the advantage of quick action and a higher degree of integration. From this "visceral brain" the endometrial vascular network may be suddenly influenced by nervous pathways down the cord operating through the vertebral sympathetic system and the sacral parasympathetic outflow. The autonomic system is again intercalated into the cerebrospinal axis, and with the shifting forward of function, these centres are finally brought into relationship with the cortical function of consciousness and contact with the external world of reality through the sense organs.

So it is that highly organized mental concepts originating in the cerebrum can gather such a quantum of emotional effect, that instead of being exteriorized and dealt with by rationalization with other conscious thoughts, they are turned inwards and find expressive action at a lower level of development in somatic processes. This concept is the basic mechanism of the entity now under consideration, which is variously known as psychogenic or hypothalamic amenorrhoea, or the pituitary-shock syndrome.

Clinical Features

It is important to establish the diagnosis of psychogenic causes, as the condition is not so uncommon, it may not be recognized, and if it persists the uterus may atrophy and finally become refractory. The things which are useful in establishing the diagnosis may be listed as follows:

(1) The sudden onset of complete secondary amenorrhoea in a woman previously regular is at once suspicious. By the time patients are seen various sporadic bleedings may have been induced with hormones and these lead to confusion in deciding the actual time of onset.

(2) Organic causes should be excluded by seeking for the stigmata of endocrine disorders, and nutritional factors should be considered. The diagnosis does not rest purely on a basis of exclusion but there are positive features which are helpful on their own. The presence of other hypothalamic features, such as anorexia, loss of weight, obesity, or attacks of water retention are common enough in the absence of organic lesions.

(3) Various other features of stress are usually present. There is likely to be a good deal of general anxiety of the "free-floating" type, showing a readiness to attach itself and be rationalized into the present life situation. This may express itself in other organs or in morbid fears, perhaps of becoming toxic or insane, or in feelings of inferiority as a result of sexual and reproductive incompetence. True hot flushes of menopausal type do not occur.

(4) The history of psychic trauma coincident with the onset is, of course, the crucial point but it is just here strangely enough that the greatest difficulty may be found. The patient will often exhibit a positive amnesia, or mental resistance to knowing and describing the circumstances of the onset, and it may not be wise to approach the question directly or too early.

(5) Cases following immediately after pregnancy are of special interest. Flagrant panhypopituitarism can be recognized by symptoms of deficiency of the three main target glands, but cases are more common where these features are absent. The question may then arise whether these symptoms are a partial Simmonds-Sheehan syndrome of necrosis in which the gonadotrophic fraction is more vulnerable and has been selectively affected, whether the "strain" of pregnancy has merely provided for an accidental onset of a premature menopause, or whether the condition has been precipitated by the handling of psychic trauma associated with parturition.

Psychological Classification

Neurosis and hysteria in popular usage are elastic terms covering disorders of character and behaviour, functional disturbances of organs, and more deep-seated upsets in thinking, feeling and acting. A useful distinction may perhaps be made between psychoneurotic and psychosomatic symptom formation. They are both responses to psychological stimuli but they differ somewhat in their psychodynamics.

Psychoneurotic symptoms: Psychoneurotic symptoms more often seem to involve the whole personality structure and to serve the purpose of solving a mental equation for the patient on the basis of organized ideas and muscles controlled by the will. There is no real wish to surrender the symptoms and the patient may be said to be taking sides with the illness. She may manipulate the environment to support the presence of the disability, and in a childish way gain a secondary advantage from the extra interest and attention.

Case 1

A patient aged 46 had swelling of the abdomen, sensations of movements, morning sickness, feelings in the breasts and had seen only a slight show in 5 months. She stated that her husband was extremely happy that she was pregnant. She was cheerful and convinced that she was pregnant, although on examination there was no evidence of it. Her only pregnancy had occurred 5 years previously when she was about 40. She had a strong maternal instinct, and had hoped and tried for more children since. The only child developed leukaemia and after a period of decline died 5 months previously when her symptoms began. Her friends were greatly surprised by her behaviour after the death of the child for she displayed remarkable equanimity in the bereavement, and her mind instead of showing the expected grief became pre-occupied with her symptoms of pseudocyesis.

The irregularity was not due to the impending menopause as menstruation later returned.

Such a case illustrates how a quantum of feeling may be equated to a purposive collection of symptoms, and how childishly naïve one portion of the mind can be in allowing another part to stand over it. It might require only a step further for a patient to complain of amenorrhoea by denying to herself the presence of menstruation which should be plainly visible to her senses. Caution is necessary in dealing with a negative feature like amenorrhoea which is hard to confirm by examination.

Psychosomatic symptoms: Psychosomatic symptoms on the other hand are based on a simpler but more primitive mechanism and the condition is sometimes known as a vegetative or organ neurosis. Amenorrhoea as a symptom is usually of this nature, and rarely on the alternative hysterical mechanism. As a result of an experience which is severely traumatic in the psychological sense that it exposes the ego to extreme danger or degradation, a quantum of emotional feeling is driven inwards, or the affect is "locked up". It would seem that the quantity of emotion may be so large, or so concentrated in intensity, that it is denied outward expression in thought and action, and is dammed up, split off from its context of memory in the exciting circumstances, and finds expression in a disguised and attenuated form in bodily symptoms. Anxiety is said to be "fear spread out thin". The symptom represents some aspect of the body's total reaction to fear, and is in that sense an anxiety equivalent. The amenorrhoea may be regarded as one of the somatic manifestations of congealed fright. The anxiety, which is not bound in the symptoms but is set free, is not attached to its appropriate context in memory or time, and this part of it is said to be "free-floating".

The symptoms usually predominate in one system of organs such as the genitalia, but commonly there are other facets, such as vasomotor symptoms, sweating, giddiness, nausea, palpitation, and unexplainable subjective feelings. This easily leads to the symptoms being secondarily invested with false rationalizations as to their meaning, and "cover causes" being made to explain them. The symptoms, however, serve no useful purpose, they have no content or meaning in the analytical sense, and they are not exploited for secondary gain, nor for social reasons in interpersonal relationships. The patient recognizes the symptoms as a handicap and would willingly part with them, unlike the psychoneurotic who, while protesting too much, may show an indifference to their presence and take pains to retain them, sometimes by extraordinary subterfuge. They are detrimental in that they keep certain vertebral sympathetic functions over-excited and parasympathetic actions inhibited in a chronic, distorted and unaccountable preparation to fight or flee.

Treatment

To the patient, amenorrhoea gives concrete evidence of an organic disorder, and when no such lesion can be offered the gynaecologist is made to feel completely helpless in front of the subject. The majority of cases are of short duration, perhaps only an irregularity of rhythm, and the cause-and-effect relationship is still linked in the patient's mind so that the condition is cured with the efflux of time. Common causes are grief from death or illnesses of relatives to whom there is an emotional attachment, change of environment, persistent situational stress, or a circumstance which has left an acute fear of pregnancy.

Interrupted rhythm and scanty or excessive flow may occur as variants of the stress reaction so that there is a gradation from amenorrhoea to menorrhagia. Sudden overwhelming and concentrated anxiety is likely to produce amenorrhoea, while persistent milder attenuated stress is likely to result in menorrhagia and rhythm disturbance. Treatment should not be undertaken lightly in the well-established cases because if it fails the patient is more deeply marooned in her illness, but in milder cases it may be sufficient to relieve the persistent stressful situation. The treatment attack is made from two directions, hormones and psychotherapy, either of which may be sufficient, but together they have a synergic effect.

Hormones: Pituitary gonadotrophins would appear to be the most rational but they are disappointing, and the secondary hormones, oestrogens and progesterone, offer more success. Uterine bleeding may be produced from a

secretory endometrium by an oestrogen-progesterone sequence over 28 days, or this effect can be produced from a proliferative endometrium by a block dose of oestrogen alone. Provided the uterus is sensitized with a small dose of oestrogen, a progesterone-withdrawal bleeding may be produced, and this has the property (if not the advantage) of causing bleeding when the time is shortened and the dose expanded, the changes in the endometrium being vascular rather than structural. This is the basis of the short-time, high-dosage, or condensed technique. Methods exist which may be called condensed, semi-condensed, and natural phase-sequence courses. The last is the most useful for induction of rhythmical bleeding in well-established cases.

It will be realized that the bleedings produced are merely end-results in a cycle, and are not necessarily at first true menstruation arising from ovarian function. Success may result from the increased growth and vascularity of end-organs in the lower genitalia, from the reciprocal action of periodic inhibition and release, a sort of pumping action or "rebound" phenomenon of the two fractions of the pituitary gland, or to abreaction of psychic tension at the highest level where endocrine and nervous systems interact. The sight of blood demonstrates to the patient the presence of functioning genital organs, it puts back on the ego "the badge of femininity". The process is analagous to making a clock tick by shaking it. Starting from below and using chemical hormones in the soma we have agitated a rhythm in the brain stem above.

Psychotherapy: It may be convenient next to look from above down and see what this second method can offer from without to the patient as a whole. Starting with the external world of reality and the conscious thought material derived from the sense organs, we might hope to arouse ideational processes in the cortex, retrace and blend them with some memory associations, perhaps throw in a pinch of emotion, and finally effect a synergic coalescence in the brain stem. Mental processes are not static but dynamic phenomena. Consciousness itself with its various degrees and qualities is a precipitate from interacting cross currents, a mere veneer resting on deeper layers.

The capacity to maintain a state of equilibrium in such a system has been likened to a block of ice, nine-tenths submerged in fluid. Degrees of consciousness may similarly be likened to a hydrometer settled to a measured depth in fluid, or perhaps to a fisherman's floater poised upright but partially submerged by the weight of the bait, hook, and sinker (Fig. 1).

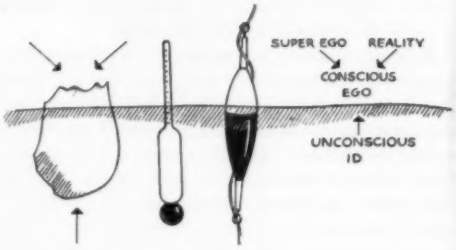

FIG. 1

In the Freudian sense the state of consciousness at any moment of time is a dynamic phenomenon resulting from the interaction of conflicting forces, and has been likened to an iceberg mostly submerged in fluid. It may be compared in a similar way to a hydrometer, or fisherman's floater, subject to adjustment in a vertical axis according to the balance of forces, and rocked about by winds and currents.

The position taken up in the vertical or transverse direction is the result of the pressure in the atmosphere, the density of the water, and the weight of the substance, but its poise may be affected by processes outside and in the longitudinal direction. What catches the eye of the observer from outside may be determined by the intensity of light which flits over the landscape, the force of winds which rock it from above, or submarine movements which agitate it from below. In like manner the mental make-up in the present is the product of an interplay of dynamic forces, some being outside the immediate present situation and residing in a longitudinal or historical sense. The mind is an instrument in which things separated at a distance in time can simultaneously interact with one another in the present.

We may, just for convenience of thinking, resolve the situation into spatial and temporal components, repression being the force which

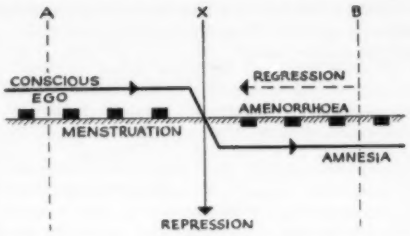

FIG. 2

At point A before the onset of amenorrhoea, the patient may be considered in normal health with the conscious ego in a state of normal poise. At point B in the here-and-now situation, the personality has undergone a change, one factor being a tendency to amnesia. The crucial point of repression at X is indicated by the time of the onset of amenorrhoea, the rhythm of which serves as a natural chronometer. To reach this point the patient's memory must be regressed in a longitudinal or temporal direction to the circumstances and feelings at that time.

acts transversely like the buoyancy of the floater, regression acting longitudinally like the clock (Fig. 2). At point A, the person before the disability may be considered to be in a state of normal adjustment between the pressure of conflicting forces; in Freudian terms, the instinctive urges from the unconscious, the exigencies of the conscious world of reality, and the strictures of the moral conscience. At point B, representing the patient with amenorrhoea in the here-and-now, the conscious part of the ego has assumed a new state of poise between the conflicting forces, it has lost something to an expansion of the unconscious. We might say by analogy that the density of the water, the pressure of the atmosphere, or the winds which blow across, have caused the iceberg to readjust itself in depth or spin on its axis, or that the sinker is on the bottom, the floater is awry and drifting, and it can be adjusted only by lifting bodily and transporting longitudinally to deeper or calmer water.

As a result of the balancing of this equation, a subtle change occurs in the personality, which would be apparent to an astute observer familiar with the patient in the before and after situations. A quantum of affect in the form of anxiety and some of its somatic concomitants seem to be left over, one of which is the amenorrhoea. When the patient's mental processes are dissociated in this way no amount of effort by the patient at point B can easily effect an alteration, nor can attempts at persuasion on an intellectual level from outside, expand or alter the ego in any way without reference to the crucial point of change at point X somewhere between.

This point of psychic trauma is localized in time by the first missed period (or by the incident or labour), and its content will often be found to contain a severe threat, sometimes linked with dangers of sex and reproduction. At this point, the patient has been overcome, inhibited, and regressed in a direction of immaturity by a fearful experience, a condition of recovery from which is a splitting off of the memory of the experience. It is as if mental processes functioned thereafter in two separate compartments, the immediate present and the significant past. Any attempt to recall the memory or perhaps reproduce the menstrual period with which it is associated, would constitute a threat to reactivate the original anxiety. The amnesia for the past is serving a protective function in keeping the subject from being overwhelmed with anxiety in the present. We might say that the floater is kept in the shadows from the light of conscious attention which flits over the surface of the landscape.

The mechanism by which the affective experience is handled at X is regressive and primitive, an ostrich-like flight into ignorance, almost a type of partial decerebration. Conserving the blood in the body by amenorrhoea might be a goal-directed striving at a primitive vegetative level, but it serves no useful purpose in the present reality situation. As Wengraf (1953) states, it is a form of mobilization to meet an emergency which is "oddly antiquated, as if a modern city were to defend itself against air attack by raising the drawbridge over a moat". An interchange of symptoms for amnesia may in some cases be made through point X. It will be necessary for the patient to undergo a superficial regression in a longitudinal, historical, or temporal direction, to recover the memory of events in the life situation which surrounded the first missed period, and perhaps feel some of the emotional affect which was turned inwards and

became locked up as the amnesia developed externally. To gynaecologists trained in the disciplines of surgery and pathology it may seem odd that objective symptoms may be resolved on the basis of an interpersonal relationship in a particular type of interview, that is by communicating with the patient's mind instead of applying trauma or chemicals to the soma. The means by which this may be accomplished are by serial discussions, perhaps assisted in some cases by the hypnotic relationship.

(1) *Serial Interviews:* The result is achieved at a superficial level by the patient remembering, ventilating, and verbalizing the traumatic circumstances. While in the consulting room she is taken from point B to point A and back again through point X, with some reassurance and hormonic support in the background.

Case 2

A graduate who had majored in philosophy saw no period for 2 years after childbirth and in spite of treatment by her obstetrician. Circumstances were favourable and the first interview was prolonged, during which there was much release of emotion. She had married well, but against the wishes of her father who was a rigid professional man, and she kept certain of the circumstances from him. When she was near term, she came to stay near at hand with her only brother. He had not fulfilled the expectation of following in his father's footsteps, but took to horses, gambled, and fell into financial trouble even worse than the family knew. He came home drunk and late, abusive, destructive, and violent. The frightened and humiliated patient was taken to hospital next morning with ineffective pains which lasted several days before delivery. The only grandson was not received warmly with her parents. Menstruation returned the day after interview, perhaps by coincidence.

(2) *Hypnotic Assistance:* For those who have the ability and inclination to enter into a closer relationship, certain hypnotic techniques may in some cases be used to advantage. The first way in which this medium may be used is by direct suggestion. Advantage is taken of the state of abstraction and muscular relaxation which is induced to implant post-hypnotic suggestion which takes hold with the force of conviction.

Case 3

A woman, aged 24, was introduced personally by her medical attendant from a country centre, her story being as follows. The families on both sides were of some local prominence, and there was interest in the marriage and its successful outcome. Pregnancy occurred 3 months after marriage and its progress was favourable until 6 months of gestation when an influenzal attack occurred and movements ceased. A policy of expectancy was rightly pursued for some months, but inwardly the patient felt considerable concern. After some delay, the patient was put in hospital by a consultant elsewhere, and the uterine contents were expelled after medicinal stimulation. She was altogether unhappy about losing the baby and was inclined to project the blame on to her family doctor.

The menses had not returned and the patient changed her attendant to a younger and more recent graduate in the town. Three withdrawal bleedings were induced with oestrogen-progesterone "two shot" injections, after which she saw one spontaneous period and entered into her second pregnancy with better expectations and considerable confidence. It transpired, however, that at term she was unexpectedly found to have a breech with extended legs, delivery was altogether difficult, and the second baby was lost. There were various cross currents of family opinion but the patient retained considerable loyalty to the younger doctor. When the menses as before had not returned she was again given injections, but this time she developed a local allergic skin reaction at the site, presumably due to the oil medium. They could not be continued and amenorrhoea persisted thereafter for another year.

The patient was depressed, torn between various loyalties and conflicting opinions, and there was talk of taking her abroad for treatment. She was healthy, morose rather than anxious, but with a strong underlying desire for children. She was given a full course of cycle regulation on the natural phase sequence. During the periodic appointments which necessitated travelling at monthly intervals, sometimes when the bleeding was present, the hypnotic relationship was developed and deepened as she was a good subject. The aim was direct removal of symptoms by post-hypnotic suggestion, explanation of the past and very direct reassurance of the future, with an emotional colouring. There was considerable change in temperament of the patient, menstruation was resumed and she subsequently had a successful pregnancy.

Summary

(1) Some cases of secondary amenorrhoea are related in time to psychic trauma, either a persistent stressful situation, or an incident of a higher degree of intensity but more circumscribed in location.

(2) The tendency to amnesia necessitates a prolonged and detailed study of the experiences, impressions, and life situation of each patient.

(3) In this particular psychosomatic disorder the presence of the menstrual rhythm serves as a natural chronometer; the time of inter-

ruption indicates in advance to the attendant the focal point of disturbance, which is the arena of therapy to which the patient's attention and any psychotherapy must be directed.

(4) This objective somatic symptom may in some cases be resolved by using hormones for cycle-regulation, combined with psychotherapy for synergic support.

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THE PELVIC PAIN SYNDROME

THE study of pelvic pain in women has remained difficult because there have been lacking in respect to it the types of knowledge that have been used to define most medically recognized entities. No generally acceptable aetiological agent has been found. There is no characterizing pathological lesion and no measurable physiological deviation from the normal. The condition must, therefore, be defined for the present by its symptomatology and physical findings.

CLINICAL CHARACTERISTICS

Two independent series of patients with the pelvic pain syndrome have been studied in our institution and the characteristic symptoms set down from an analysis of these 200 case histories. There results the picture of a clinical entity which seems to be definite enough to deal with.

The patients are nearly, but not all, in their twenties or thirties and are usually married. The majority have had one or more children, although there appears to be a relatively high incidence of abortion and infertility.

The characteristic symptom is, of course, pain of some type, usually lower abdominal and bilateral, dull, constantly present, variable in intensity.

Beside this pain, there are other types such as low backache, secondary dysmenorrhoea, a sense of rectal pressure and dyspareunia. A variety of minor complaints occur with sufficient frequency to make it appear that these are a part of the condition.

The physical findings are characteristically vague and difficult to evaluate. There may be tenderness on one or both sides of the lower abdomen. Bimanual examination will disclose parametrial tenderness, best demonstrated when the examiner displaces the uterus anteriorly or to one side. Ovarian tenderness and perhaps enlargement may also be present. In some, but not all of the cases, there appears to be hypersecretion of the endocervical glands.

A characteristic of the disorder is the high incidence of what we may call psychosomatic complaints. This has been repeatedly mentioned in the literature and will be referred to in greater detail later in this report.

The foregoing description must serve as the basis for defining the entity we are discussing, but provisionally only. Our efforts should be directed to the finding of a better criterion for identification, an aetiological agent, a measurable physiological aberration or a pathological lesion.

THE NATURE OF THE UNDERLYING DISORDER

The "pelvic pain syndrome" has been the object of the gynaecologist's interest for well over a century, but the large literature is obscured by the multitude of names which have been applied to it. These have tended to follow concepts of disease currently popular at the time of the proposal of each special designation.

In reviewing the terms that have been proposed, with the pathology implied by each, one can see that there has been a gradual change from the concept of a chronic inflammation, through ideas suggesting a neuralgia or a vascular congestion, to the modern concepts of autonomic nervous system dysfunction and

psychosomatic medicine. Many of these terms are not mutually exclusive and such a general designation as "the pelvic sympathetic syndrome" may well include the idea of a hyperalgesia as well as of a vascular disturbance.

It seems indeed possible in the group of patients with pelvic pain that one is dealing with several distinct disorders having a somewhat similar symptomatology but with a variable underlying lesion or physiological disturbance. In one type, evidence of vascular disorder is almost apparent from clinical observation. In others such signs are lacking and all that is detectable on physical examination is the exquisite tenderness of the utero-sacral ligaments. Since such cases are at times observed after the menopause, it must be conceded that there are certainly some cases in which a vascular disturbance is not the immediate cause of symptoms and, for this second type, one must fall back upon some neurological theory of hyperaesthesia or referred pain.

Several observers, including the speaker, have somewhat recklessly suggested that the condition might indeed be a single one and that a phase of vascular disorder is followed after many years by one of fibrosis of the arteries and parametrial tissue.

If this were true, then in patients with these different clinical appearances we would be looking at the same disease in different phases of its evolution.

The principal reasons for believing a vascular factor to be important in many patients with pelvic discomfort may be arranged as follows:

It is evident that the vessels of the pelvic organs are capable of rapid and radical alterations in their physiology in response to various nervous stimuli, some of a specific, i.e., sexual character, others probably non-specific. An attempt has been made in our department to measure pelvic blood flow, or at least, its changes. Variations in pelvic blood flow, as measured by determination of thermal conductance of the vaginal wall, are quite evident during the course of an hour's interview, and seem referable to the subject matter discussed (Duncan and Taylor, 1952). This response, which was admittedly quite predictable, is at least indicative of factors which may produce physiological and, eventually, perhaps pathological change in the pelvic circulation.

The second type of evidence is that seen within the pelvis in the occasional case of this type which comes to surgery. In the typical case, in an operation carried out perhaps for retroversion and descensus, there is an evident increase in the amount of peritoneal fluid in the pouch of Douglas; the peritoneum has a glistening, oedematous appearance; the ovaries are perhaps slightly swollen and the uterine fundus is enlarged, soft and of an unusually deep red colour. The apparently oedematous condition of the uterine lining sometimes receives apparent confirmation from the histological appearance of the endometrium, although the process of the routine laboratory preparation of tissue usually destroys such evidence of hyperaemia or increased tissue fluids.

The sometimes excessive pre-menstrual changes in the breasts, pain, tenderness and evident enlargement, seem a somewhat analogous condition. Such alterations on account of the rapidity of their appearance and disappearance seem certainly based on vascular changes. The association of such breast symptoms with pelvic pain in the series of patients appears too striking to be simply coincidental.

It is our view then that a physiological disorder of the pelvic circulation is a prominent feature of at least a considerable portion of these cases.

The Aetiological Factors

Having presented some evidence on the nature of the process underlying the "pelvic pain syndrome", it is necessary to consider briefly the possible aetiological factors. Here one has an initial choice between (*a*) an infectious agent, (*b*) an hormonal disorder or (*c*) psychological factors acting through the pelvic autonomic nervous system on certain target organs such as smooth muscle. Opinion seems to be tending more and more to the last of the three.

Interest in the psychological and psychiatric background of these patients in our Department began a number of years ago and in 1952 Duncan reported his studies on a series of 36

patients. His conclusions were that a large percentage of the patients with the pelvic pain syndrome are emotionally ill and that this disturbance precedes and is not the result of the pelvic discomfort. Consistent findings in the patients of Duncan's series included emotional immaturity, strong dependent needs and inadequacy when called upon to perform the functions of a woman, either sexually or maternally.

A somewhat more fundamental investigation has now been completed in our Department by Dr. Lothar Gidro-Frank, a psychiatrist, with the co-operation of Miss Thelma Gordon, a psychologist. Their study concerned 40 patients with the pelvic pain syndrome and a control group of 25 women taken at random from the ante-partum clinic. This investigation was based on "semi-structured psychiatric interviews", ranging in number from one to sixty, and a series of psychological examinations, including figure drawings, the Rorschach and thematic apperception tests. The complete report of their work is in press, but brief reference to their more important findings is in order.

Precise psychiatric diagnosis could be made on a number of women of both the pelvic pain and the control groups. The high incidence of psychiatric disorder among the supposedly normal women of our ante-partum clinic was surprising and disturbing. Nevertheless the pelvic pain group was much more seriously affected for, with these the diagnosis of schizophrenia was made four times as compared to none for the controls and "severe neurosis" was present in 20 of the 40 patients and in only 4 of the controls.

"Neurotic and psychosomatic symptoms", other than those classified as "gynaecologic", were also far more frequent in the experimental group. The neurotic symptoms included phobias, compulsions, hysterical paralysis, headaches, joint pains and others. The incidence of psychosomatic complaints, such as allergies, migraine and colitis was also many times higher, occurring in 27 of the 40 pelvic pain cases and in only 6 of the 25 controls.

With regard to life situations discontent and dissatisfaction were characteristic of the pelvic pain group. Twenty-five of the pelvic pain group and only 6 of the control group indicated dissatisfaction with their husbands. Twenty-six of the pain group as compared with 10 from the pre-natal clinic were critical of their households.

The emotional history of previous pregnancies indicated that these could be classified as disturbed in 25 of the experimental patients as compared with 9 in the control group. Pregnancies were classified as "disturbed" if dissatisfaction, resentment, fear or depression had been obviously present.

The psychological test that was applied to the largest number of patients was that based on figure drawings, the subject being asked first to draw a person and then one of the opposite sex. The pairs of drawings resulting could be classified into four groups which ranged from the infantile with no sexual differentiation of Group I, through those with considerable distortion, to the relatively mature, differentiated figures in Group IV. The results indicated a high proportion of unusually infantile drawings for the patients with pelvic pain indicating "an immature self concept with flight from maternal and sexual roles".

Conclusion

One may now perhaps begin to see some order developing out of the confused problem of the pelvic pain syndrome.

(1) The study of symptomatology and physical signs permits the characterization of a rather definite entity.

(2) Some evidence exists that the disorder is at first a functional disturbance of vasomotor, perhaps secretory and perhaps sensory components of the pelvic autonomic nervous system.

(3) Patients with this condition undoubtedly suffer from emotional and other psychiatric disturbances which probably represent the starting points of the pelvic autonomic nervous system disorder.

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Treatment of the Climacteric Woman

The majority of women pass the climacterium without complaint; the minority who develop the menopausal syndrome may present difficult problems of diagnosis and treatment. I have made my share of errors in treating climacteric symptoms. Women at the menopause should be regarded with the same wariness which we use on the first encounter with a patient who appears to be an obvious neurotic. Through the years I have learned to ask myself: "Are this patient's complaints pathological, psychological, or physiological?" Despite wariness flushes, sweats, palpitations and jitteriness have proved to be thyrotoxicosis; lassitude, obesity and irritability have proved to be early myxoedema; bloating and indigestion have proved to be gall-bladder disease; and scanty, regular vaginal bleeding has proved to be pelvic carcinoma. All the symptoms mentioned are ones which occur frequently in menopausal women. Many of them are considered to be physiological concomitants of the climacteric and waning ovarian function. Most of them can be produced by psychological factors. If the patient were not in the menopausal age group, would the pathological significance be recognized immediately and the stumbling block of physiological inconsequentiality be avoided?

Women present themselves with menopausal symptoms earlier nowadays than they did ten to fifteen years ago. This is the result of much being written about the menopause in popular magazines. If a woman has no symptoms she thinks she should have some because the magazines say so. This is the fertile field from which grow the psychosomatic aspects of the menopause, and our diagnostic problems.

Many practitioners prescribe oestrogens routinely when a patient first presents herself with symptoms which might be attributed to the menopause. Unfortunately too often the prescription is given without taking a thorough history and without making a physical and pelvic examination. The doctor is busy and the menopausal patient can be an unmitigated nuisance. I deplore the practice of prescribing oestrogens indiscriminately as being contra-physiological, damaging psychologically, and certainly aggravating to possible undiagnosed pelvic pathology. Ovarian activity must come to an end, and the body will adjust to the deprivation. Attempting to forestall or prolong the adjustment is not physiological, and is no kindness to the patient.

Now that the menopausal syndrome has been adopted into the family of psychosomatic medicine, we must educate doctors to the unpalatable fact that this means more time, rather than less, must be spent in considering the symptoms of the climacteric woman. Explanation, understanding, and mild sedatives must replace freely prescribed oestrogens. However, a potential danger lurks here because the fact that the doctor is paying sympathetic attention to her symptoms may enhance them in the eyes of the patient. One must endeavour to maintain a balance between the physiological and psychological aspects at this point; this is a much more difficult and time-consuming procedure than prescribing oestrogens at a first visit.

Gynaecologists fall heir to patients in their sixties who are still bedevilled by flushes, sweats, sore breasts and occasional vaginal bleeding. The patients tell the same story of having been given "change of life pills" fifteen to twenty years previously; when they stop taking the pills the climacteric symptoms return so they begin taking the pills again. These women present a real problem of therapy, and certainly a curettage should be done to rule out intrauterine pathology in those who are having excessive or sanguineous vaginal discharge. I have operated upon such a patient, aged 67, whose uterus was the size of a sixteen-weeks pregnancy with active adenomyosis although both ovaries appeared to be completely atrophic; she had been taking oestrogens for twenty-three years.

There is an interesting paradox which I have observed on examining women who have been on oestrogens for many months. The introitus and vaginal mucosa appear kraurotic, as though the mucosa, too long subjected to oestrogenic stimulation, had undergone premature senility. When the women have overcome the habituation to the "change of life pills", the mucosa regains its normal appearance.

I approve of stress being laid on the psychosomatic aspects of the menopausal syndrome. But let us not lose sight of the fact that it is primarily a physiological readjustment. Explanation, particularly with recall of the psychological and physiological difficulties the woman underwent at the menarche, will be invaluable in helping her to understand her present discomforts, the causes underlying them, their cyclicity, and their temporariness. If one can persuade the patient to accept the dictum that each flush means one less to go, her battle is more easily won.

DR. L. J. GOLUB (Philadelphia)

PSYCHOGENIC DYSMENORRHOEA

DYSMENORRHOEA requires no introduction to this audience.

Among 16,183 girls who attend sixteen Philadelphia Public High Schools 30·2 per cent have frequent dysmenorrhoea, 37·4 per cent have occasional dysmenorrhoea and 32·4 per cent are free of this complaint.

In common with many other gynaecologists and obstetricians in the United States, I felt that dysmenorrhoea was largely psychogenic in origin. In 1952 I suggested to the members of the Special Education Committee of the School District of Philadelphia that we conduct a study to ascertain whether dysmenorrhoea could be treated by mass psychology.

Between 1st January and 1st June, 1953, 1,049 girls of school Ax (experimental) and school Ac (control) were given prescribed general exercises. The girls in the experimental school were told that the exercises would relieve dysmenorrhoea, while no mention of dysmenorrhoea was made in Ac, the control school.

When the results of this study were examined, I was very much surprised at the absence of any evidence that dysmenorrhoea could be treated by "mass psychology" and suggested that the study be repeated in two other Philadelphia Public High Schools for a longer period of time and that the teachers in the experimental school emphasize more strongly that the general exercises the girls were performing would relieve dysmenorrhoea.

The second study with school Bx (experimental) and Bc (control) and 1,657 girls participating was carried out from 1st November, 1953 to 1st November, 1954; the results were similar to those of the first experiment. The complete study included 2,706 girls.

The various schools, experimental and control, did show some differences in the number of teachers involved and in the percentage of white and non-white students. Ac has 8 physical education teachers; and 60 per cent of the student population is non-white. Bc is a vocational technical school with 3 physical education teachers and about 34 per cent non-white students. Ax has 7 physical education teachers and 17 per cent non-white students. Bx has 11 physical education teachers and no non-white students.

All girls in both studies received the same routine body conditioning exercises as part of their physical education instruction. At the beginning and end of each of the time periods a general health questionnaire was distributed to each student asking among other medical conditions about the current presence or absence of dysmenorrhoea. Throughout the school year the teachers of the experimental schools frequently stated that the exercises would help to eliminate dysmenorrhoea. At the control schools there was no mention of dysmenorrhoea.

It is to be noted that the incidence of dysmenorrhoea was not the same at every school at the start of the experiment. The two control schools (Ac and Bc) and one experimental school (Ax) were comparable with a combined incidence of 42·9 per cent; the incidence of dysmenorrhoea at one experimental school (Bx) was significantly lower—28·5 per cent. A possible partial explanation for this is the absence of non-whites in this school, dysmenorrhoea being more common in the non-white. None of the schools showed any significant change in the incidence of dysmenorrhoea from the beginning to the end of the experiment.

Of those free of dysmenorrhoea at the start of the study 12·4 per cent to 20·6 per cent suffered from dysmenorrhoea at the end of the

experiment. School to school differences cannot be explained on the basis of psychological suggestion because: (*a*) no mention was made of any efficacy of exercise in eliminating dysmenorrhoea and (*b*) there was no consistency in the school-to-school differences as evidenced by the fact that the two experimental schools had the highest and lowest percentages of all four groups.

There was no significant school-to-school difference in the proportion of girls completely relieved of their dysmenorrhoea. Hence, there is no evidence that dysmenorrhoea can be alleviated by the type of psychological suggestion employed in this study. Altogether, 23·1 per cent were relieved of dysmenorrhoea; this may be taken as an estimate of the proportion of cases which resolve themselves "spontaneously" over an interval of six months to a year.

Currently at the Jefferson Medical College Hospital in Philadelphia, a research project is being conducted in dysmenorrhoea in regard to its gynaecological, hormonal, orthopaedic and psychiatric aspects. Dr. Coleman V. Kovach is the psychiatrist in charge.

Of one hundred patients examined thus far, 70 per cent were adolescents and 15 per cent were adults suffering from primary dysmenorrhoea. One adolescent and 14 adults had secondary dysmenorrhoea.

Eighty-six of the one hundred patients were seen one or more times for psychiatric evaluation. No important emotional factors were found in 73 per cent. Of the 27 per cent who did demonstrate psychologic factors 18 were classified as "primary dysmenorrhoea" and 5 as "secondary dysmenorrhoea".

Psychiatric factors in these 23 patients were labelled thus: 1 had incipient schizophrenia; 1 had marked hostility and also suffered from migraine headaches; 1 had a marked guilt reaction resulting from an illegitimate pregnancy; 1 had conversion hysteria; 2 had strong fears of marriage and concomitant desires for pregnancy; 2 had fears of pregnancy (1 in which the fear followed an operation for an ectopic tubal pregnancy); 3 had a mixed type of psychoneurosis; 3 had marked dependency reactions; and 9 had emotional immaturity reactions.

In September, 1959, a psychiatrist will perform a control study of both dysmenorrhoeic and non-dysmenorrhoeic girls participating in the Philadelphia School District.

There are several reasons for the common tendency to label all dysmenorrhoeics as psychoneurotics: (1) The voluminous literature and editorials favouring the psychosomatic aspect and supported by a few case reports; (2) one study on the threshold of pain which has been frequently cited; and (3) the fact that patients who present themselves with dysmenorrhoea are frequently nervous and upset.

However, if a person has frequent attacks of pain he may become nervous and develop a low threshold of pain but which of the two—low pain threshold or pain (in this case dysmenorrhoea)—is cause and which effect cannot be specifically determined. While there are undoubtedly psychoneurotic dysmenorrhoeic patients, there is by no means general agreement on their relative frequency.

MR. J. B. BLAIKLEY (London)

PSYCHOGENIC MENORRHAGIA

THE term "Psychosomatic Illness" has provoked much opposition, but at the same time it has high-lighted the important part emotional factors can play in the production of illness. Many of these illnesses, it seems to me, are related to the person's make-up, and to that extent the term "Diathesis", which was popular when I was a student, is perhaps an alternative; but it is hard to decide to what extent it is the physical make-up and to what the emotional that predisposes to certain disorders and illnesses. In the disorders under discussion the emotional factors appear to play a predominant part in producing physical symptoms. Certainly as gynaecologists we must always be awake to the importance of these factors.

My own interest has been centred in particular on menorrhagia or perhaps I should rather say uterine bleeding, and in the treatment of many of my patients I have, in the last 15 years, had Dr. O'Neill's help. Uterine bleeding can take very various forms if it arises as a result of

emotional factors. One can have a true menorrhagia, heavy loss with rather prolonged periods, or a shortened cycle. I think that some of the intermenstrual bleedings which last perhaps only an hour or two or maybe a day or two are psychogenic in origin. I suspect that emotional factors render that particular woman abnormally responsive to a change in the oestrogen level in the blood stream. It is particularly important to recognize that psychogenic menorrhagia is not at all uncommon, particularly in young women in their early twenties. Very often it can be cured by simple psychotherapy and by any good doctor, because the patient herself has considerable insight into the mechanism of her bleeding; she links up the bleeding with emotional difficulties, although perhaps she does not fully appreciate the relationship.

I remember Mr. Frank Cook once telling me that he had asked Professor Heyman in Stockholm: "What do you do with all your menorrhagias?" "Oh," he replied, "I send them to a good doctor—he cures them by talking." I think that is very true, and it has been emphasized today. What strikes me most about many of these patients is the severity of the bleeding and in particular the long spells of bleeding that can occur. One of my patients—she has been a patient of either Dr. O'Neill or myself off and on for the past 14 years—once bled continuously for 50 weeks out of 52. This was followed later by a long spell of amenorrhoea when she was in a depressed phase; at the moment Dr. O'Neill is treating her for anorexia nervosa. She has certainly shown us a number of different aspects of psychosomatic gynaecology.

One can very often, but not always, find other features suggestive of a psychogenic disturbance, for example, insomnia, being easily fatigued, inability to concentrate, depression, agitation, although these symptoms are not always obvious either to the patient herself or to her friends. Curettage is of diagnostic value only in excluding other causes. Typically no abnormal changes are found in the endometrium, and I believe bleeding occurs at any and every stage of the cycle. It is my belief that the mechanism is vasomotor and that vasodilatation is produced through the autonomic nervous system. I have met patients where the onset of uterine bleeding is instantaneous under emotional stress, or if not instantaneous very nearly so. The cause of the stress is sometimes quite trivial, as, for example, one woman who told me she bled every time her employer spoke sharply to her. I remember she bled—and bled quite freely—as I was about to examine her and she said that it was due to emotional tension. Another told me she bled every time she was watching a film if it became too emotional and too tense. It has been my experience that the severe cases are those in which continued emotional conflict concerns the husband, fiancé, lover, children or others very dear to the patient; in many the sexual aspect looms large.

It has been clearly demonstrated that under emotional stress many organs become hyperaemic and congested, and bleed readily. In 1949 Dr. Howard Taylor discussed the possibility that organic changes could result but I gather today that he is still very uncertain, as I think we all must be. In such illnesses, however, as peptic ulcer or ulcerative colitis, there is little doubt in my mind that stress plays a large part in the aetiology. Some physicians think that the vasomotor changes are primary and that they lay the mucosa open to ulceration and inflammation from non-specific causes, and it is not beyond the bounds of possibility that organic disease does follow on the changes brought about by psychogenic factors. But where is the proof that we are all looking for? We have not up to date found it.

When talking on this subject I always like to point out that the first recorded case of psychogenic bleeding is in St. Luke's Gospel, Chapter 8, where one reads: "And a woman having an issue of blood twelve years, which had spent all her living upon physicians" (which I think is very well put) "neither could be healed of any, came behind Him and touched the border of His garment: and immediately her issue of blood stanched." No doubt out of her faith she got peace of mind for the first time in many years. The story is most illustrative. It is extraordinary how quickly the bleeding can stop if the patient's difficulties can be alleviated, and that alone I think points to a psychogenic control in these cases.

Mr. G. W. Theobald (Bradford)

This discussion is evidence that this generation has re-discovered the fact first reported by a Mr. Fernandez of London, in the first decade of last century, that gynaecological symptoms may occur without discoverable organic lesions. This observation was first published by Gooch in 1829 and expanded by Ferguson in his introduction to the 1859 edition of Gooch's book. Richard Bright postulated in his classical writings on the disease named after him that undetectable metabolic changes preceded the structural changes, and modern studies show that sensation can be modified by such factors as temperature, hormonal and electrolyte imbalance, synapse resistance and oxygen tension. There is, therefore, no reason why gynaecological and other symptoms should not occur apart from detectable organic lesions. The very fact that herniation of the lumbar and cervical discs was unrecognized a quarter of a century ago, and that causalgia (with no organic basis) can be cured by anaesthetizing a sympathetic nerve ganglion, should make us wary of attributing to "psychosomatic stress" and "psychosomatosis" symptoms which we do not fully understand. The fault may lie in us and not in our patients and I am satisfied that these symptoms, and in particular pelvic pain, are far less vague and capricious than has been suggested by Dr. O'Neill and Mr. Bourne. Neither can I agree that dyspareunia on deep penetration is most often encountered in grande multiparae.

I have been profoundly interested in this problem for over a quarter of a century and in 1936 postulated that the "ultimate control of every function in the body is vested in the central nervous system" and that every rhythmic function of the body, including menstruation, ovulation, pregnancy and parturition, was controlled by a centre or centres in the hypothalamus. It follows, and I have constantly affirmed this belief (Theobald, 1936, 1941, 1946, 1951 and 1953) that all gynaecological symptoms are amenable to psychotherapy, and that even the date of the onset of the menses can be altered at will by hypnotic suggestion. Because symptoms can be cured by psychotherapy it does not follow either that they arose because of "stress" or that the hypothesis on which the treatment was based is correct. Psychoanalytical and other forms of psychotherapy may cure a patient of her symptoms, but so may faith, whether exercised at Lourdes or in some "Divine Healing" service in this country.

I confess I am sceptical of terms such as "psychosomatic", "psychosomatosis", and "stress". Are the women presumed to have souls, or is the psyche to be regarded as a conglomeration of chemical molecules and notably of nucleotides? What is meant by somatic? Is it used in contra-distinction to the areas supplied by autonomic nerves? Such a view would be retrograde for it is now recognized that sensory nerves travel in sympathetic pathways and that large numbers of sympathetic and parasympathetic nerves travel to the cerebral cortex.

In my view "mind" and "spirit", which may have a profound effect on emotion and stress, cannot be described in known terms, and my remarks will be confined to "brain". Its ultimate development is limited by hereditary factors and may be damaged as we heard yesterday by birth trauma. A child born blind, deaf, and dumb is liable to sleep its life away, and the various images we form which make up our personalities are built up both on sensory impulses and chemical influences. The formative sensory impulses reach the brain not only through the ears, eyes, palate, and skin, but also from the joints and viscera, and it is clear that our sensation of pain bears but little resemblance to the pain signals which provoke it. The chemical influences are not limited to hormones, for our very existence is dependent on the oxygen tension of the blood and on the osmolarity of blood traversing the internal carotid arteries. It therefore seems reasonable to suggest that some gynaecological symptoms, such as vaginismus, may arise mainly in the brain, whereas others, such as dyspareunia, arise most commonly in the periphery. It is idle to imagine that disturbed function in sensory nerves will of necessity be accompanied by gross and detectable pathological changes. Indeed, carcinoma and fibromyomata cause symptoms merely because they stretch or press on sympathetic, and later somatic nerves.

In conclusion I would state my belief that a high proportion of these symptoms could be prevented by postnatal care, for a much higher percentage of these cases occur in hospital than in private practice. Not more, and probably less, than 50 per cent of hospital patients receive postnatal care of some sort or another, and I think it probable that an increase in such care and in the observance of elementary hygienic rules, together with better nutrition and housing, would almost empty the gynaecological out-patient departments.

Let us learn what we can from psychologists, but it would be unpardonable to develop a vast gynaecological psychological-psychiatric empire (for the number of such patients is large) with all the expense involved, when simple suggestion, over-stimulation of nerve endings in the neighbourhood of the internal os uteri, and the liberal use of local anaesthesia can cure the majority of these patients in the out-patient department. The only thing which would be worse would be to send the women home telling them that their backache, dysmenorrhoea, dyspareunia, urinary symptoms and iliac fossa pain were due to "nerves" and stress, and that they must "jump out of it". I prefer the concepts of cerebral inco-ordination and of the pelvic sympathetic syndrome. I acknowledge that most of these symptoms can be cured by suggestion and by hypnosis but believe that it is cheaper, simpler and nearly always as effective, although not easy, to use the therapy I have advocated.

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Dr. Frederick Lane (Manhasset, New York)

I have here a survey which I have just conducted in the United States. We sent a questionnaire to 1,800 members of the American College of Obstetrics and Gynecology, and I am pleased to record that 900 responded. I shall not burden you with all the statistics but merely enumerate those which concern this morning's discussion. One of the questions we asked was: "What is your biggest problem in the practice of office gynaecology today?" We had some very interesting, some significant and many humorous replies. Those who stated "psychosomatic problems" were third on the list, the first being trichomoniasis and the second all forms of vaginitis. I may say, in support of one of your other speakers, that lack of time on the part of the physician was ninth on this list. I might also add that, after listing the first ten answers statistically, there were some 140 men who responded variously, some, for example, stating: "unhappy women"; others, "the failure of psychosomatic therapy", and "marital problems"; one man stated "talkative women", and another merely "women" in quotation marks. From the viewpoint of the problem of the doctor himself, there is this answer: "I am getting too old and too tired and too irritable myself." Another doctor from Baltimore answered "Parking for myself and my patients". I might say I did not exactly appreciate the man who wrote "An excess of this type of questionnaire". Finally, I would say that the results of this enquiry will be published very soon. I hope later to obtain help in this country to make a similar study and eventually to compare the two, the practice of gynaecology here and in the United States.

Mr. J. V. O'Sullivan (London)

Mr. Theobald in his brilliant summing-up said many of the things I was going to say. There is one point, however. Recently I had occasion with other colleagues to try to determine the sex of an individual who I thought was a straightforward under-developed woman —they decided that she was a man! They told

me for the first time in my life that we gynaecologists and obstetricians must now look upon the brain as an endocrine organ. Perhaps if we did move the brain from the super ego down to practical reality we might make a little more progress.

DR. DESMOND O'NEILL (London) (*Summing Up*)

I HAVE been very much interested and educated to hear my colleagues here. Of Mr. Bourne, I need say no more than that it is an honour to share a platform with him. He has formed the ways of thought of many doctors and gynaecologists, among them my friend and colleague Norman Morris who helped me do the enquiry at University College Hospital.

We seem to be in some difficulty over the term "psychosomatic". Let me make it clear that I have no quarrel with the concept which I believe was introduced in the United States by Dr. Dunbar who was a pioneer in this field and for whose work and also that of Dr. Wolfe of New York I have the very highest regard. America is in this particular field certainly very far ahead of us and I have (metaphorically speaking) sat at the feet of Dr. Wolfe who is a sound general physician with his feet firmly planted on the ground. I pay tribute to the work of our American colleagues in their research.

I enjoyed Dr. Taylor's very interesting and diverting account of pelvic congestion. I think that is a terribly important aspect to study; it is a different approach but how dull it would be if we all had the same point of view—if we all talked about "psyche". How important it is that somebody should investigate the neurophysiology and biochemistry of these many reactions as he is doing. I suspect that the women he is seeing with pelvic pain are rather like the ones we see here and if we try to stand back from them and look at this whole arena of human suffering, we can see that pelvic pain in women is one form of a very widespread disorder, a good deal of which does not come to the doctor at all. We would do well to remember that. Some goes to the faith healer or the priest and a good deal of it is treated by correspondence!

By and large the family doctor is the first port of call and he treats "according to his diathesis" as John Blaikley says. The most important drug in medicine today (if I can use that phrase again) is the doctor himself. How he handles tension pain and menorrhagia and all the other things depends on himself. Some doctors become terribly irritated and throw the patient out, others can listen, others feel disposed to use physical methods—well, good luck to them! I quite agree with the speaker who said that physical methods must be used—of course they must. If, in the rough and tumble of out-patient practice physical methods can help the patient more quickly and more effectively, let us by all means use them. I have no time at all for the ivory tower analyst who uses only psychoanalysis; it is very good for him to come down to earth and meet the people who are dealing with the rough and tumble.

Going back to Dr. Taylor, I should think with respect that some of his patients at any rate are cases of what we call tension pain and that one is chasing a wild hare in looking for a physical lesion. If one looks hard enough, something can be found! By all means study the physical side but I do feel that we must pay attention to the social and personal background. As regards another of his points—let us quantify, let us measure, let us bring it down to figures—this seems to me to be one more sign of number work. As formal religion declines, people need something to worship and what they tend to worship nowadays is statistics. With due respect, what we need is not figures but logic. Some of the greatest discoveries in the history of science have not been made by numbers or quantification; but that is in no way to detract from Dr. Taylor's work, which I admire.

As regards Dr. Black's contribution on the menopause, I would remark that it was Donovan of Rochester, New York, who wrote the paper that impressed me most on the subject. He examined quite a large series of women referred to him with "the menopausal syndrome" and at the end of his study he reached this conclusion: that a woman does not come to the doctor at the time of the menopause unless she is emotionally upset. I decided to test this so I selected at random a patient from a routine gynaecological

clinic, sat down with her and spent a good deal of time. Summarizing very shortly: she had a tension depression. She had been on oestrogens and about that I could not agree more with Dr. Black. I took her off oestrogens and put her on a homœopathic dose of seconal. With that and the emotional ventilation, she settled down. That was a case of the so-called menopausal syndrome which on closer examination turned out to be rather more a tension state with depression. I am not denying the existence of the menopause as a biological occurrence, of course, but it should be a natural event. Why should it cause symptoms? All it does, I think, is to make a woman slightly more vulnerable. If she is tense already she becomes more tense. I am not being dogmatic; please do accept that I am just giving a point to you. I realize all too well how much blank space there is in our knowledge of the subject and how humble we ought to be.

I had the honour and pleasure of working with John Blaikley for many years—he introduced me to this question of menorrhagia. His original paper was a pioneer contribution in this country and his understanding of patients has taught me a great deal; he has taught me also how much can be done by the man, the doctor, if he uses the right approach. One does not have to be psychiatrically trained; what counts ultimately is to be of assistance.

I should like to express again my gratitude for being allowed to speak to you—that a psychiatrist should be asked to address this gathering is, I think, a sign of the times.

OESTROGEN METABOLISM

BY

SIR CHARLES DODDS, *M.V.O.*, M.D., F.R.C.P., F.R.S.
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IN the first instance I should like to thank you for inviting me to have the privilege of opening this discussion. In the very brief period that I have at my disposal we can conveniently commence at the year 1923 because prior to that there was no method of accurately standardizing the hormones of the ovary. As you will remember, in the year 1923, the American workers Allen and Doisy described what they called the oestrous vaginal smear test which has become the standard biological method of estimating oestrogens. That test, I may very briefly remind you, entails taking ovariectomized laboratory animals such as rats and mice and studying their vaginal histology by smear; it is possible to induce by an active preparation the appearance of the keratinized plaques which are characteristic of oestrus, and by suitable distribution of dosages and a sufficient number of animals, this method can be made highly quantitative. This established the oestrogens on a firm basis from a biological point of view but unfortunately very little advance was made in their chemistry because they were found to be practically unpurifiable. The oestrogens of the 1923 period were deep-coloured oils extracted from the ovary by means of volatile solvents and they resisted purification. It was not until 1927 that the German workers Aschheim and Zondek made the astonishing discovery that the urine of certain pregnant animals contained, amongst many other things, oestrogens in large quantities. One of the favourite animals was the pregnant mare and it was found that oestrogens in the urine of the pregnant mare were already purified, so to speak, by their passage through the kidney. It so happened that chemical work on similar lines had developed in a way that made it possible to apply that knowledge to the material of Aschheim and Zondek. To proceed very quickly, by the nineteen-thirties crystalline preparations had been prepared from the urine of pregnancy and a number of these substances had been characterized chemically. There were 5 oestrogens present in the urine of the pregnant mare, namely: oestrone, oestradiol (which is present not in the urine but in the follicular fluid of the pregnant mare), oestriol (discovered by Professor Marrian), equilene and equilenine. Oestradiol was soon found to be the most powerful and when converted into an ester, oestradiol benzoate, it was very suitable indeed for the treatment of gynaecological conditions. From about 1932 gynaecologists were provided for the very first time with a highly active preparation and, as you know, a great deal of literature sprang up dealing with the treatment of menopausal symptoms by oestradiol benzoate.

In 1938 an entirely new development from the clinical point of view burst on the scene. In my laboratory we had been interested since 1930 in making synthetic analogues of these natural forms and we had struggled along manufacturing chemicals which had definite oestrogenic activity but very low potency, in fact, quite unsuitable for clinical use. But in 1938 we were able to synthesize a group of substances that were not only active when injected but were also highly active when given by mouth. These substances were stilboestrol (which was the first and is I think the one that is still most used throughout the world), hexoestrol (which is the same as stilboestrol but with its double bond hydrogenated) and

dienoestrol (which has also been used clinically quite extensively). These substances can replace the naturally-occurring oestrogens in every way both quantitatively and qualitatively.

A number of other developments in the synthetic oestrogen field have not found much clinical use. There are compounds derived from tri-phenolethylene, which have a low activity but are possibly stored in fat depots and thus have a very prolonged action. Other compounds in which a hydrogen atom has been replaced with a halogen (chlorine or bromine) have been used to a small extent. Various other substances have also been tried but there is very little literature on them. By and large I think it is fair to state that stilboestrol, hexoestrol and dienoestrol are the only ones of which there is appreciable practical experience.

A third group of oestrogens lies midway between the synthetic and the natural. These are modified natural oestrogens of which the best known is ethinyl oestradiol (where an ethinyl group has been added synthetically to the 17 position of the naturally-occurring oestradiol). This substance is very highly active when given by mouth.

We now come to the real point of this meeting —to discuss the question of metabolism. There is one great difference between the metabolism of the naturally-occurring oestrogens and the synthetic and that was shown many years ago by Bernard Zondek. He found that if one takes an animal, injects into it a large quantity of oestrone, kills it shortly afterwards and extracts it for oestrone, the oestrone has completely disappeared, that is to say it has been metabolized. If one does the same experiment with stilboestrol, one finds that practically the whole of the stilboestrol can be recovered. A great deal of work has been done on the metabolism of the naturally-occurring oestrogens, particularly in Professor Marrian's laboratory. We are shortly going to have the privilege of hearing Dr. Brown speak so I shall not deal with this aspect except to say that the naturally-occurring oestrogens are very rapidly modified and metabolized in contra-distinction to the synthetic ones. We have made a very detailed study of the metabolism of the synthetic oestrogens and have recently completed work in which we have studied the metabolism of triturated hexoestrol. We have found that by giving this to rabbits in both physiological and abnormally large doses, one can account for some 98 per cent of the administered oestrogen; that is to say, as far as one can tell, there is no metabolic breakdown at all. Several experiments have been done with carbon-labelled stilboestrol and also with labelled halogenated triphenolethylene derivatives, and we believe that these substances simply circulate in the body. We believe, indeed we are sure, that they are absorbed from the alimentary canal and are subsequently excreted, 90 per cent being accounted for in the urine and faeces. This may explain the toxicity of the synthetic oestrogens as against the natural; they linger longer and are presumably not destroyed by the liver as are the naturally-occurring hormones.

A very interesting development has occurred in the United States where stilboestrol is used extensively for the raising of steers for beef-producing purposes. The animals are implanted with stilboestrol tablets and stilboestrol is added to the feed to bring the animals to maturity at a much earlier date. It is estimated that some 98 per cent of the beef in the United States is derived from animals treated with stilboestrol, and this has caused great anxiety lest, since the substance is excreted unchanged, the pastures might in time become saturated with this highly potent material. But, strange to say, that does not occur because, despite its great stability in the animal body, it is immediately destroyed by soil bacteria.

Let us conclude with one interesting side of the oestrogens which should be of great interest to practising gynaecologists, and which is just beginning to dawn on us in the experimental field. This arose from the very interesting observation of a group of workers in Australia who found that sheep in certain areas became sterile. The sterility was due entirely to the ewes which were examined post-mortem and were found to have a condition of the uterine mucous membrane very similar to that produced by excessive oestrogen treatment; it was therefore assumed that there must be in the pasture a powerful oestrogen. These pastures consisted of clover which was collected and extracted, and

found to contain a very powerful oestrogen known as genistein. It is very similar to stilboestrol with an oxygen bridge at the top and it is present in practically all vegetables and in grasses. There is no doubt that a considerable amount of oestrogen is consumed in the food in this form. We may well have to consider, when we think of oestrogens and oestrogen metabolism in the human subject, the sort of oestrogenic background we get in our food from this and similar types of substance. This work is not very well known in this country, but a number of surveys are now being made into the distribution of such oestrogens in vegetable foods. We know little or nothing about the metabolism of these substances but it would appear that they have the same stability as stilboestrol in the body.

With those opening remarks I should like to conclude and to leave the metabolism of the naturally-occurring oestrogens to my distinguished colleague Dr. Brown.

THE METABOLISM OF OESTROGENS AND THE MEASUREMENT OF THE EXCRETORY PRODUCTS IN THE URINE

BY

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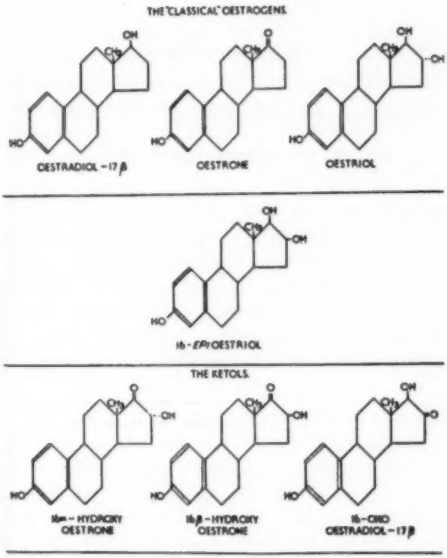

FIG. 1
Oestrogens isolated from human urine.

INTRODUCTION

PRIOR to 1955, only three oestrogens had been isolated from human sources. These were oestradiol-17β,* oestrone and oestriol. Their chemical formulae are shown in Figure 1. Studies in which each of these oestrogens was administered to human subjects showed that oestradiol and oestrone are rapidly interconvertible in the body and are metabolized irreversibly to oestriol. Only a small proportion of the dose could be accounted for in the urine as oestradiol, oestrone and oestriol (Schiller and Pincus, 1943). Oestradiol and oestrone were regarded as the primary oestrogenic hormones but, at that time, no correlation had been demonstrated between the amounts of these produced in the body and the amounts of the three oestrogens excreted in the urine. Since 1955, however, considerable advances have been made in our knowledge of the intermediary metabolism of the oestrogenic hormones and of the quantitative significance of the metabolites excreted in the urine. These advances have been mainly the result of work started some years earlier by Professor Marrian and his co-workers in Edinburgh, and by Dr. Gallagher and his co-workers at the Sloan-Kettering Institute in New York. The new developments can be listed under the following three headings:

(1) The discovery of new oestrogen metabolites in urine.
(2) The use of oestrogens labelled with radioactive carbon for studying the intermediary metabolism of the oestrogenic hormones, and
(3) The development of reliable methods for measuring oestradiol, oestrone and oestriol in human urine.

* Throughout this paper "oestradiol" implies "oestradiol-17β".

I. THE DISCOVERY OF THE NEW OESTROGEN METABOLITES IN HUMAN URINE

The discovery of the new oestrogens in human urine has been facilitated by a number of factors.

Many of them had already been synthesized in the laboratory by Drs. Huffman and Gallagher and their co-workers before they were shown to be natural products. Many, but not all, of them give a pink colour in the Kober reaction. This colour reaction is highly specific for the natural oestrogens and, in fact, was instrumental in the discovery of all the new oestrogens isolated by Professor Marrian's group. Isotopic labelling of oestrogens has provided a specific test for identifying their metabolic products. This method has contributed to the identification of four of the new urinary oestrogens.

16-epioestriol (Fig. 1)

The discovery of the first new oestrogen, 16-*epi*oestriol, was reported in 1955 by Marrian and Bauld. Its existence was indicated by the finding of a fourth Kober chromogen during the chromatographic separation of oestradiol, oestrone and oestriol from human pregnancy urine. This was isolated and identified as 16-*epi*oestriol, a compound which had previously been synthesized from oestrone by Huffman (1942).

The Ring D α-ketolic Oestrogens (Fig. 1)

Following some speculations on possible intermediates in the conversion of oestradiol to oestriol and 16-*epi*oestriol, Marrian and his co-workers (Marrian, Watson and Panattoni, 1957; Marrian, Loke, Watson and Panattoni, 1957) isolated a 5th Kober chromogen from a ketonic fraction of human pregnancy urine and showed it to be 16α-hydroxyoestrone, a compound which had previously been prepared synthetically by Leeds, Fukushima and Gallagher (1954). Meanwhile, Levitz, Spitzer and Twombly (1956) identified 16-oxo-oestradiol-17β in the urine of subjects following the administration of isotopically labelled oestradiol, and later Layne and Marrian (1958) isolated this compound from human pregnancy urine. 16-oxo-oestradiol-17β had been prepared synthetically by Huffman and Lott (1948). It now seemed likely that 16α-hydroxyoestrone was the immediate precursor of oestriol, and that the then unknown compound 16β-hydroxyoestrone would be the corresponding precursor

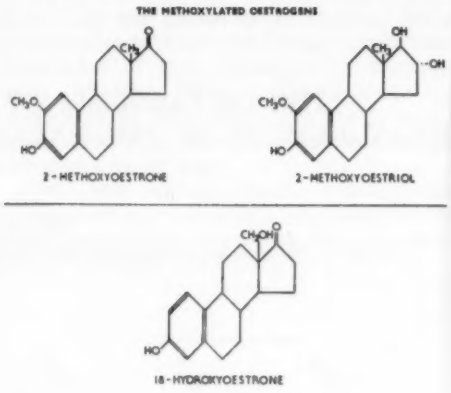

FIG. 2
Oestrogens isolated from human urine (continued).

of 16-*epi*oestriol. The search for 16β-hydroxyoestrone was facilitated by its recent synthesis by Biggerstaff and Gallagher (1957). Subsequently, it was identified by Layne and Marrian (1958) in human pregnancy urine and by Brown, Fishman and Gallagher (1958) following the administration of isotopically labelled oestradiol.

18-hydroxyoestrone (Fig. 2)

During the search for the foregoing compounds, Professor Marrian's group isolated two more new Kober chromogens from human pregnancy urine. One of these has been identified as 18-hydroxyoestrone (Loke, Watson and Marrian, 1957; Loke, Marrian, Johnson, Meyer and Cameron, 1958). The other has not yet been fully characterized (Marrian, 1959).

2-methoxyoestrone and 2-methoxyoestriol (Fig. 2)

During their studies on the metabolism of isotopically labelled oestradiol and oestrone, Dr. Gallagher and his co-workers isolated a radioactive fraction from urine which did not correspond to any of the known oestrogens. The properties of this new derivative indicated that it was a monomethyl ether of 2-hydroxy- or 4-hydroxyoestrone. Subsequently, synthesis of all the possible compounds showed that it

was 2-methoxyoestrone (Kraychy and Gallagher, 1957a, b). Later, 2-methoxyoestriol was also identified in the urine of subjects who had received isotopically labelled oestradiol (Fishman and Gallagher, 1958). Its discovery indicates that the other 2-methoxylated oestrogens such as the 2-methoxylated ring D α-ketols are also likely derivatives to be found in urine.

II.—The Use of Isotopically Labelled Oestrogens for Studying the Intermediary Metabolism of the Oestrogenic Hormones

A number of American workers have used isotopically labelled oestrogens for studying the metabolism of the oestrogenic hormones in man. The most detailed investigations of this nature have been those of Dr. Gallagher and his group. Their findings are summarized in Figures 3 and 4.

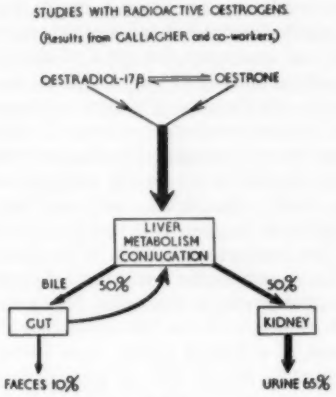

FIG. 3

The metabolism of oestradiol and oestrone (from Brown, Fishman, Hellman and Gallagher, 1959).

STUDIES WITH RADIOACTIVE OESTROGENS
(results from Gallagher and co-workers)

Administered Oestradiol-17β

100

Urine (65) | Faeces (10) | Unaccounted (25)

100

Neutral + Phenolic (75) | Acidic (5) | Spent Urine (20)

100

		References
—oestradiol-17β	5	Beer and Gallagher (1955a, b)
—oestrone	10	Beer and Gallagher (1955a, b)
—oestriol	30	Beer and Gallagher (1955a, b) Brown, Fishman and Gallagher (1958)
—16-*epi*oestriol	6	Brown, Fishman and Gallagher (1958)
—16α-hydroxyoestrone —16-oxo-oestradiol-17β	7	Brown, Fishman and Gallagher (1958)
—16β-hydroxyoestrone	3	Brown, Fishman and Gallagher (1958)
—2-methoxyoestrone	3	Brown, Fishman, Hellman and Gallagher (1959)
—2-methoxyoestriol	1	Fishman and Gallagher (1958)
—unaccounted	35	

All values shown are approximate only; they vary considerably from subject to subject.

FIG. 4

The excretion of oestrogen metabolites in the urine.

These workers administered small doses of 16-^{14}C labelled oestradiol and oestrone to human subjects and measured the rates of elimination of the radioactivity in the urine, faeces and bile. Confirming the findings of earlier workers, they showed that the metabolic products of oestradiol and oestrone are indistinguishable and that the two must therefore be rapidly interconvertible in the body. Oestradiol and oestrone are metabolized in the liver to a variety of products which are conjugated mainly with glucuronic acid. These conjugates are excreted partly in the bile and partly in the urine. Working with patients in whom all the bile could be collected by means of a biliary fistula, they found that approximately 50 per cent of the administered radioactivity was excreted in the bile within the first 12 hours and 50 per cent in the urine. The metabolic products appeared to be the same in both bile and urine (Brown, Fishman, Hellman and Gallagher, 1959). The bile normally drains into the gut and most of the biliary oestrogens are re-absorbed from there and returned to the liver, where they are excreted again partly in the bile and partly in the urine. Eventually, approximately 65 per cent of the administered radioactivity was found in the urine and 10 per cent in the faeces (Beer and Gallagher, 1955a, b). Approximately 25 per cent of the dose was unaccounted for.

The urine was then incubated with the enzyme, β-glucuronidase, extracted exhaustively with ether, and the ether extract was divided into the "neutral plus phenolic" fraction and the "acidic" fraction. The radioactivity present in these two fractions and in the spent urine was measured. Figure 4 summarizes the results obtained from a number of individuals. Approximately 75 per cent of the radioactivity present in the original urine was found in the neutral plus phenolic fractions, 5 per cent in the acidic fraction and 20 per cent in the spent urine (Beer and Gallagher, 1955a, b). The neutral plus phenolic fraction, which contains all the known oestrogen metabolites, was further processed by countercurrent distribution and paper chromatography and separated into a number of distinct fractions. Many of these fractions were identified as the known oestrogens by their chromatographic behaviour and by reverse-isotopic dilution. The relative amounts of these oestrogens present in the neutral plus phenolic fraction, as judged by the amounts of radioactivity found in their respective fractions, are shown in the figure. The values have been abstracted from a number of publications from the Sloan-Kettering group. They vary considerably from subject to subject and those shown should be regarded as representative only. Thirty-five per cent of the radioactivity in the neutral plus phenolic fraction is still unidentified. A small amount of this will be contributed by 18-hydroxyoestrone which was not characterized by these workers. However, it is reasonable to believe that more metabolites of oestradiol have yet to be discovered and that sooner or later all the administered dose will be accounted for.

III.—Methods for Measuring Endogenous Oestrogen Excretion

The foregoing results were obtained by the use of isotopically labelled oestrogens. Methods have not yet been devised for measuring all these urinary oestrogens when they are derived from endogenous sources. Such a method is likely to be extremely complicated and laborious. However, reliable chemical methods suitable for day-to-day routine use have been devised for measuring three of the urinary oestrogens, oestradiol, oestrone and oestriol. The two most widely used of these methods were developed in Edinburgh by Brown and Bauld working under Professor Marrian (Brown, 1955a, later modified by Brown, Bulbrook and Greenwood, 1957a; Bauld, 1956). These two methods differ in the chromatographic systems employed for the separation and purification of the oestrogen fractions, but in both the oestrogens are measured colorimetrically by a modification of the Kober colour reaction. According to the available evidence, the three oestrogens can be measured with reasonable precision by either method in urines containing as little as 3 μg of each of them per 24-hour excretion (Marrian, 1956; Brown, Bulbrook and Greenwood, 1957b; Gallagher, Kraychy, Fishman, Brown and Marrian, 1958). This sensitivity has proved adequate for studying the excretion of oestradiol, oestrone and oestriol throughout the normal

menstrual cycle, in gynaecological disorders, during pregnancy, and following the administration of oestrogens to human subjects. The remainder of this paper and the following paper by Professor Kellar will deal with the results obtained by these methods. From now on, the term "urinary oestrogens" implies oestradiol-17β, oestrone and oestriol only, and the term "total urinary oestrogens" implies the sum of these three.

IV.—Urinary Oestrogen Excretion Following the Administration of Oestradiol, Oestrone and Oestriol to Human Subjects

When measuring the amount of oestrogens excreted in the urine, it is useful to know what this represents in terms of the original oestrogens secreted in the body. As with the study of the intermediary metabolism of the oestrogenic hormones, this information can be obtained by administering oestrogens to human subjects and measuring the amounts recovered in the urine. Results obtained from this type of experiment are shown in Table I.

Table I

Urinary Oestrogen Excretion Following the Intramuscular Administration of Oestrogens to Human Subjects. Results for Oestradiol-17β, Oestrone and Oestriol Only
(Brown, 1957)

Oestrogen Injected	Number of Experiments	"Total" Additional Oestrogen Excreted as Percentage of Injected Dose	
		Mean	Range
Oestradiol-17β ..	6	23	13–35
Oestrone	6	22	15–38
Oestriol	6	79	73–85

"Total" oestrogen = oestradiol-17β + oestrone + oestriol. The results are corrected for methodological losses.

Following the administration of either oestradiol or oestrone, the fraction of the dose recovered in the urine as the three oestrogens ranged from 13 to 38 per cent with a mean of 22 per cent.* Therefore if it is assumed that oestradiol and oestrone are the primary oestrogenic hormones, then, as a first approximation, the amounts of these secreted per 24 hours by the ovaries and adrenals can be calculated by multiplying the total urinary figures by a factor of 5.

Table II shows the relative proportions of the three oestrogens recovered in the urine following the administration of oestradiol, oestrone and oestriol and also the corresponding figures for the excretion of endogenous oestrogens during the follicular and luteal phases of the menstrual cycle. Following the intramuscular injections of

Table II

Relative Proportions of Oestradiol-17β, Oestrone and Oestriol Excreted in the Urine (A) After the Intramuscular Injection of Oestradiol-17β, Oestrone and Oestriol, and (B) During the Ovulatory and Luteal Phases of the Menstrual Cycle
(from Brown, 1957)

A

Oestrogen Injected	Amounts of Individual Oestrogens Excreted as Percentages of "Total" Oestrogen Excreted (Mean ± S.D. for 6 Subjects)	
Oestradiol-17β ..	Oestradiol-17β	15 ± 4
	Oestrone	41 ± 8
	Oestriol	44 ± 11
Oestrone	Oestradiol-17β	10 ± 3
	Oestrone	44 ± 6
	Oestriol	46 ± 8
Oestriol	Oestradiol-17β	0
	Oestrone	0
	Oestriol	100

B

Phase of Menstrual Cycle	Amounts of Individual Oestrogens Excreted as Percentages of "Total" Oestrogen Excreted (Mean ± S.D. for 8 Subjects)	
Ovulatory phase ..	Oestradiol-17β	15 ± 5
	Oestrone	40 ± 8
	Oestriol	45 ± 12
Luteal phase ..	Oestradiol-17β	14 ± 4
	Oestrone	38 ± 8
	Oestriol	48 ± 11

"Total" oestrogen = oestradiol-17β + oestrone + oestriol.

* This figure agrees closely with that for oestradiol, oestrone and oestriol given in Figure 4,

oestradiol and oestrone, approximately 13 per cent of the "total" oestrogens recovered in the urine was oestradiol, 42 per cent was oestrone and 45 per cent was oestriol. These proportions were practically the same as those for the excretion of endogenous oestrogens during the follicular and luteal phases of the menstrual cycle. In contrast, the administration of oestriol led to the excretion of oestriol only in the urine. These findings support the belief that the human ovary secretes oestradiol or oestrone or a mixture of both but not significant amounts of oestriol.

V.—Urinary Oestrogen Excretion During the Menstrual Cycle

Before attempting to interpret results obtained in gynaecological disorders, it was necessary, first of all, to establish with certainty the normal range of values for the ovulatory menstrual cycle.

Figures 5–7 illustrate the results obtained. The amounts of the three oestrogens excreted rise and fall together. They are lowest during the first week of the cycle and then rise to a well defined peak (the "ovulatory peak") on or about the 13th day of the cycle. The oestrogen excretion then falls and rises again to a second maximum. This "luteal maximum" is usually lower than the "ovulatory peak" and in some women may be virtually absent. During the last few days of the cycle the oestrogen excretion falls and menstruation occurs at this time. The mid-cycle peak has been observed in every ovulatory cycle studied. Its shape is highly characteristic: it is shown by all three oestrogen fractions; the rise to the peak is usually gradual and the fall after the peak is abrupt; the rise and fall of the oestriol levels tend to lag slightly behind the rise and fall in oestradiol and oestrone levels (in Figure 5 the highest excretion of oestradiol/oestrone occurred on the 13th day while that of the oestriol occurred on the 14th day); and the interval of time between the peak and the onset of menstruation is approximately 14 days. These findings may be explained as follows: the amounts of oestradiol and oestrone secreted increase as the Graafian follicle increases in size and reach a peak just before rupture at ovulation; rupture causes a temporary arrest in oestrogen production and the output falls; growth and regression of the corpus luteum leads to the second rise and fall in oestrogen excretion. If this interpretation is correct, then ovulation should be very closely related in time to the mid-cycle peak of oestrogen excretion. Proof of this point is difficult. However, there is no doubt that measurement of the daily output of urinary oestrogens provides very useful information concerning ovarian activity and that the finding of the characteristic "ovulatory" peak is good evidence that ovulation has occurred (Brown, 1955b; Brown, Klopper and Loraine, 1958; Brown, Kellar and Matthew, 1959).

Summary

(1) At the present time, 10 metabolites of the primary oestrogenic hormones, oestradiol and oestrone, have been isolated from human urine and identified.

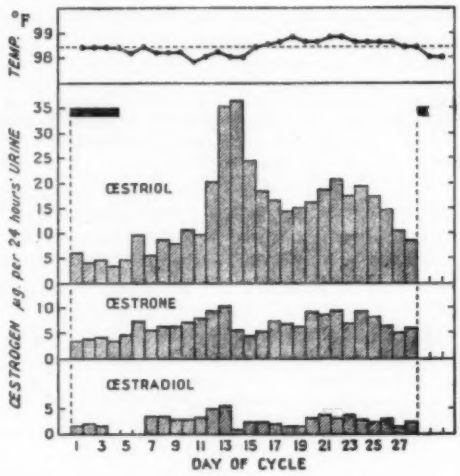

Fig. 5

Urinary excretion of oestrogens during the menstrual cycle. This Figure shows the amounts of oestradiol, oestrone and oestriol excreted per 24 hours, and also the variations in basal temperature.

■ = menstrual period.

Subject, aged 36; para-3 (from Brown, 1955b).

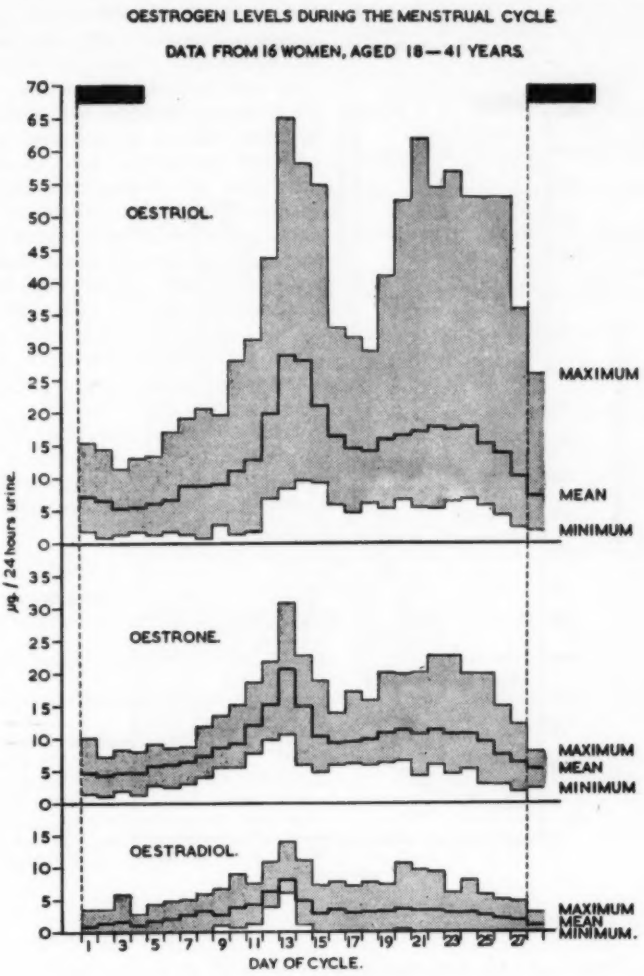

FIG. 6

Mean, maximum and minimum levels of urinary oestradiol, oestrone and oestriol excreted by 16 women, aged 18–41 years with normal menstrual cycles. The time between the onset of bleeding (day 1) and the ovulatory peak of oestrone/oestradiol varied from 10 to 18 days (mean 13 days) and between this peak and the onset of the next menstruation, from 12 to 16 days (mean 14 days). Curves were constructed by superimposing individual curves in such a way that each of the oestrone/oestradiol ovulatory peaks coincided with day 13 of the composite curves.

■ = menstruation.

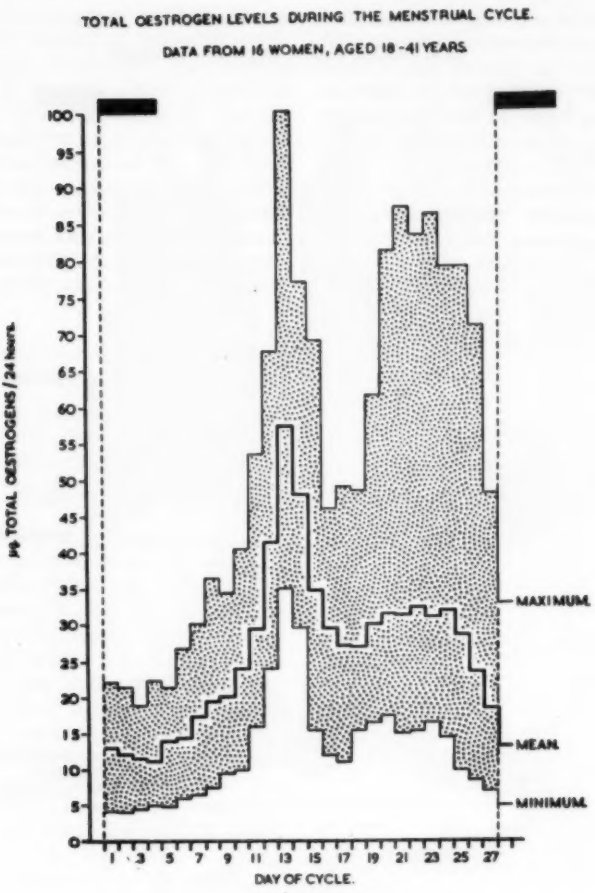

FIG. 7

Mean, maximum and minimum levels of "total" urinary oestrogens excreted by 16 women, aged 18–41 years with normal menstrual cycles. The time between the onset of bleeding (day 1) and the ovulatory peak of oestrone/oestradiol varied from 10 to 18 days (mean 13 days) and between this peak and the onset of the next menstruation, from 12 to 16 days (mean 14 days). Curves were constructed by superimposing individual curves in such a way that each of the oestrone/oestradiol ovulatory peaks coincided with day 13 of the composite curves. Results obtained by summing the values shown in Figure 6.

■ = menstruation.

(from Brown, Kellar and Matthew, 1959)

(2) Oestrogen metabolism has been studied using isotopically labelled compounds. Oestradiol and oestrone are rapidly interconvertible in the tissues and are metabolized and conjugated in the liver. The metabolic products are excreted in the urine and in the bile. Most of the biliary component is re-absorbed from the gut and excreted eventually in the urine; the remainder is excreted in the faeces. The urinary component has been further fractionated and the quantitative relationship between the 10 known metabolites and the oestrogen administered has been determined. Part of the administered radioactivity is still unaccounted for.

(3) Methods of proved reliability are available for measuring three of the urinary oestrogens, oestradiol, oestrone and oestriol. These methods provide useful information concerning ovarian activity during the menstrual cycle and the values obtained can be related to the amounts of oestrogens secreted by the ovary.

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SOME CLINICAL APPLICATIONS OF OESTROGEN ASSAY*

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GYNAECOLOGICAL CONSIDERATIONS

MUCH of our past knowledge of the role of the oestrogens has been obtained by indirect means. For instance, the administration of oestrogens to a patient with a senile vaginitis caused thickening of the vaginal skin and consequent amelioration of the condition. Their use in patients suffering from secondary amenorrhoea led to endometrial stimulation and consequent bleeding. These were rather obvious examples of oestrogen lack. In cystic glandular hyperplasia it was certain that there was a state of excess oestrogen production and the degree of myometrial and endometrial hyperplasia was good evidence of this. Certain hormone producing tumours such as a granulosal cell tumour might have a rejuvenating effect when they occurred in elderly women. In all these examples the amount of oestrogen present could be estimated in an approximate way by endometrial biopsy or vaginal smear or more exactly by biological quantitative estimations. Oestrogens have been thought to be implicated in such conditions as uterine fibroids, carcinoma of the cervix and of the endometrium, endometriosis and the like, but in these conditions any real evidence of abnormal oestrogen production has been lacking. With the introduction of the chemical quantitative methods it has become possible to measure the urinary oestrogen excretion in a wide variety of gynaecological conditions and we now have a reasonable idea of what is happening in many of them.

I.—THE POST-MENOPAUSAL PATIENT

The total mean urinary oestrogen excretion in a post-menopausal patient is of the order of 5·8 μg. per 24 hours with a range of 3·1 μg. to 8·1 μg. It is reasonably certain that the source of this oestrogen is the adrenal glands for their removal leads to a fall in oestrogen excretion to very low levels.

Post-menopausal Bleeding

During the past few years we have had the opportunity of measuring the oestrogen output in a variety of conditions giving rise to post-menopausal bleeding and the following are the sort of results we obtained.

(1) In some cases the source of the post-menopausal bleeding was a cervical or endometrial polyp and in such patients there was no alteration in the normal post-menopausal levels of excretion. Similarly, patients who have a post-

* Presented by Professor Kellar.

menopausal haemorrhage, and in whom an atrophic endometrium is found or in whom no curettings are obtained, fall into this group.

(2) *Ovarian tumours.* We have now had the opportunity of studying several patients presenting with post-menopausal bleeding and in whom a *simple ovarian tumour* has been discovered and removed. In one such patient a daily excretion of 45 μg. total oestrogen was found, falling to post-menopausal levels after the removal of a pseudomucinous ovarian cyst and hysterectomy. Extensive histological examination of the tumour failed to reveal any granulosal elements although the endometrium was typical of cystic glandular hyperplasia. In these cases it must be assumed that the stroma supporting the epithelium is functioning as an oestrogen source. We have also noted this phenomenon in *malignant ovarian tumours.* Unfortunately we have not had the opportunity of carrying out many observations on post-menopausal patients with oestrogenic ovarian tumours. One elderly patient with post-menopausal bleeding was found to have a cystic glandular hyperplasia of the endometrium and an ovarian tumour. She was excreting over 30 μg. of oestrogen daily before the removal of what proved to be a granulosal cell tumour. It will be noted, therefore, that ovarian tumours, benign, malignant or hormone-producing, can give rise to levels of oestrogen sufficient to cause endometrial proliferation and bleeding after the menopause.

Carcinoma of the Cervix

In 6 patients in our original series the cause of the post-menopausal bleeding was a carcinoma of the cervix. The mean total oestrogen excretion was 5·6 μg. daily, thus falling into the normal post-menopausal range.

Carcinoma of the Endometrium

In 5 cases the cause of the post-menopausal bleeding was found to be an adenocarcinoma of the endometrium, and again the mean total oestrogen excretion level of 5·5 μg. was that of the normal post-menopause.

In this very small series of 11 patients with carcinoma of cervix and endometrium there is no evidence of any abnormal excretion of oestrogens. This group is well worthy, however, of more extensive study and we hope we may hear of other observations this afternoon.

II.—The Amenorrhoeas

These patients form a heterogeneous group and our results of oestrogen assay can be briefly summarized as follows:

Primary Amenorrhoea. Congenital absence of the uterus and vagina. In 3 such patients it was found that there was evidence of cyclical activity of the ovaries, thus indicating that this activity can occur in the absence of the target organs.

Secondary Amenorrhoea. In one group the oestrogen excretion is low and within the post-menopausal level. The endometrium, if any can be obtained, is in a resting phase. In the majority of such patients spontaneous return of ovarian activity is unlikely and many of these patients would appear to have a premature menopause.

In the second group the oestrogen output is within proliferative levels and the endometrium shows varying degrees of activity. Most of the patients we have studied have shown a spontaneous return of menstrual function after a variable period of amenorrhoea. This grouping of patients suffering from amenorrhoea into those with a post-menopausal level of oestrogen excretion and a poor prognosis and those with a proliferative level and a better prognosis is probably reasonably accurate but it is not always correct, and we have had one patient with a low menopausal level who later had a spontaneous return of menstrual function and became pregnant.

It is important that the oestrogen excretion levels should be studied over a reasonable period of time and reliance should not be placed on a few or isolated observations. We are at present studying patients suffering from amenorrhoea with a view to analyzing the precise oestrogen/gonadotrophin relationships.

III.—Dysfunctional Uterine Bleeding

The group of patients suffering from dysfunctional uterine bleeding is a very difficult one for study as the patient requires to have

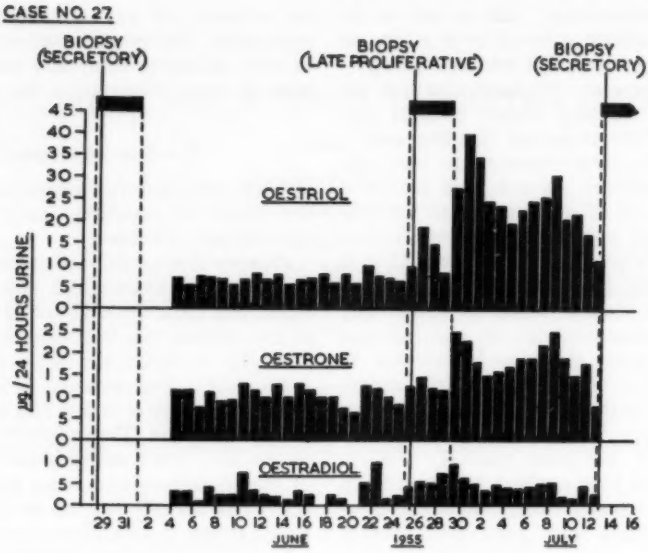

FIG. 1

Anovulatory menstruation (Brown *et al.*, 1959).

oestrogen assays over a prolonged period of time if any real knowledge is to be obtained.

Anovulatory Cycles

This is perhaps the simplest form of dysfunctional uterine bleeding and we have been fortunate in being able to study some 11 anovulatory cycles. The anovulatory cycle is characterized by the relative constancy of the total daily oestrogen excretion which varies between the range 13 μg.–30 μg. Figure 1 shows a very typical example of an anovulatory cycle with a steady oestrogen output of 20 μg. daily and followed by an ovulatory cycle.

Cystic Glandular Hyperplasia

It is not easy to obtain suitable patients suffering from cystic glandular hyperplasia for adequate study as so often some form of definitive treatment has to be given.

In the relatively few cases that we were able to study for many weeks and also in those in whom only short periods of investigation were possible, it was found that, in general, cystic glandular hyperplasia of the endometrium is associated with daily total oestrogen excretion rates of the order of 30 μg. In some cases those excretion levels were maintained for several weeks. Daily rates of over 100 μg. have been recorded.

It was noted that in some cases of cystic glandular hyperplasia the daily excretion rates, instead of remaining relatively constant, might show broadly fluctuating levels and the patient might have what were to her relatively normal periods.

Finally, it became clear that uterine bleeding in this condition might be associated with rising, falling or relatively constant levels of oestrogen excretion.

The following figures which were published in the *Journal* earlier this year depict the oestrogen excretion levels in cystic glandular hyperplasia (Brown *et al.*, 1959) (Figs. 2, 3, 4 and 5).

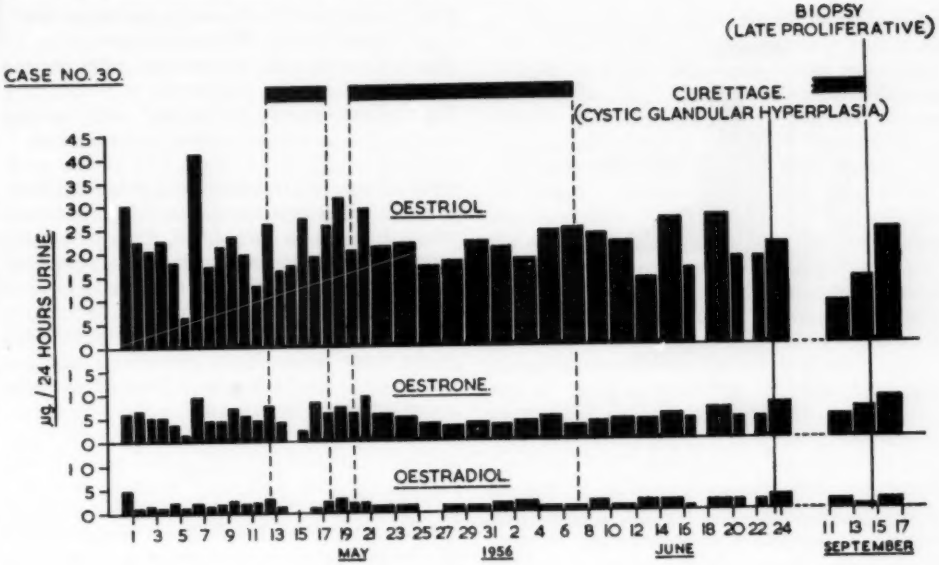

FIG. 2

Cystic glandular hyperplasia. Constant oestrogen excretion levels.

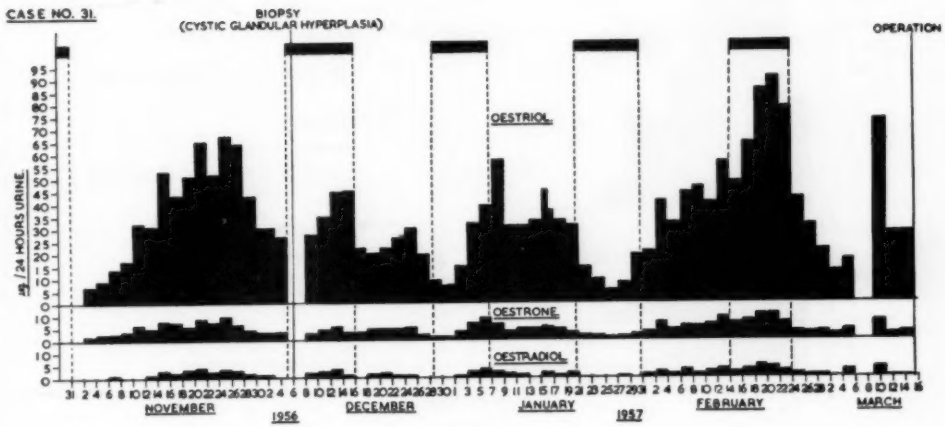

FIG. 3

Cystic glandular hyperplasia. Fluctuating excretion levels.

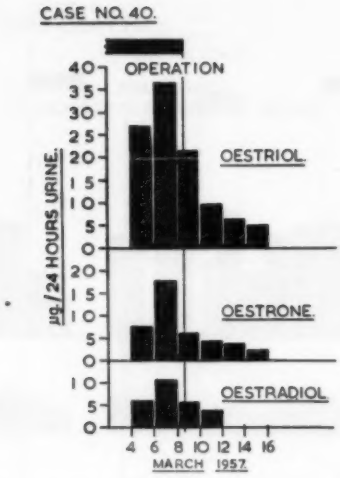

FIG. 4

Cystic glandular hyperplasia. Urinary excretion levels before and after hysterectomy.

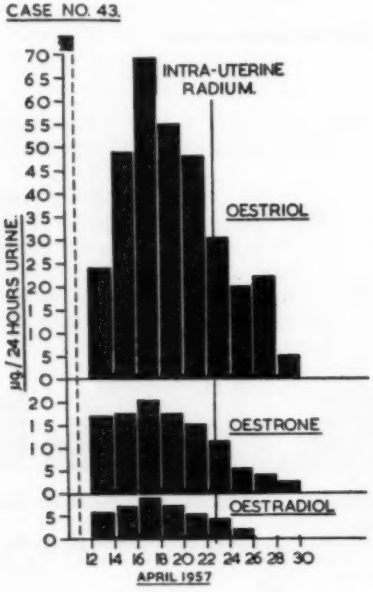

FIG. 5

Cystic glandular hyperplasia. Urinary excretion levels before and after intra-uterine radium.

Fig. 2, Case No. 30. Constant oestrogen levels.
Fig. 3, Case No. 31. Fluctuating levels.
Fig. 4, Case No. 40. Before and after hysterectomy.
Fig. 5, Case No. 43. Before and after radium menopause insertion.

Other Forms of Dysfunctional Uterine Bleeding

We do not propose to discuss this rather complicated group in any detail. Patients of this group had irregular, infrequent or heavy periods and histological examination of the endometrium showed a proliferative endometrium. In this type of case the total oestrogen excretion was usually in the range 10 μg.–25 μg. a day, i.e., proliferative phase levels. Little or no pattern of oestrogen excretion could be discerned.

DISCUSSION

Time does not permit me to discuss these results in any detail but Figure 6 shows the level of oestrogen excretion in relation to some of the gynaecological disorders studied.

In general, there was a good correlation between the oestrogen excretion levels and the state of the endometrium although there were some exceptions. Puttarajurs and Taylor (1959), in their excellent study on the relationship between oestrogen excretion and the vaginal smear, have similarly noted a good correlation but again with some exceptions.

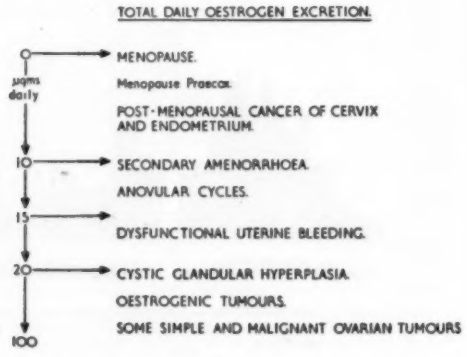

FIG. 6

Urinary oestrogen excretion levels in various gynaecological disorders.

It may be argued that the chemical estimation of urinary oestrogens will seldom be necessary for the clinician and that the study of the endometrium or of the vaginal smear will satisfy his requirements. This may well be the case.

Simplification of the chemical technique, however, will shortly allow a "routine" laboratory to offer oestrogen determinations, and there will be many patients in whom it will be useful to know the oestrogen excretion in diagnosis and in therapeutic control.

Obstetrical Considerations

Even before the first world war certain German authors had noted the presence of oestrogenic substances in the human placenta and Fellner (1912) is generally credited as being the first to note this phenomenon. In the following decades it became obvious that the placenta was indeed a rich source of oestrogenic materials and by 1930 pure oestriol had been identified in extracts of the human placenta. In 1927 Aschheim and Zondek first noted the presence of large quantities of oestrogenic substances in human pregnancy urine and in the following year demonstrated that oestrogens in the human pregnancy urine rose from about the 12th week of pregnancy to relatively high levels at term to fall to low levels in the early puerperium. In 1927 Margaret G. Smith demonstrated that the blood of pregnant human females contained a substance identical with "follicular hormone", and this reached its maximum concentration at term only to disappear rapidly in the puerperium. It is salutary for us, then, to remember that over thirty years ago it was known that the placenta was a rich source of oestrogens and that these substances appeared in the blood and urine in increasing quantities until term when they promptly disappeared. All this painstaking work had of course been dependent on the biological methods of estimating oestrogens.

In 1935 Guy Marrian and his co-workers in Toronto had developed a purely chemical method of estimating oestriol and oestrone in the urine and in that year published their now classical paper on the "Excretion of Oestrin during Pregnancy" (Cohen *et al.*, 1935). This was, we are told by our chemical colleagues, the first time that a steroid substance was accurately measured in a body fluid by a purely chemical method. At this time Marrian believed that

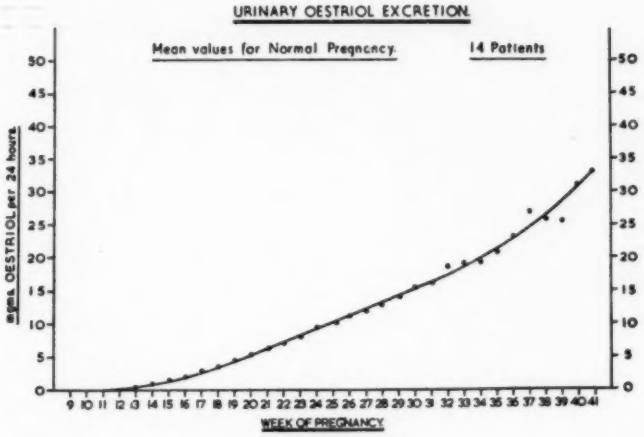

FIG. 7

Mean urinary oestriol excretion during normal pregnancy. Based on 309 observations on 14 normal pregnancies.

oestriol was excreted in a conjugated form until shortly before term when most of it was excreted in a "free" form. Years later he was to show that this was due to the fact that the urines supplied to him from late pregnancy patients by his obstetrical colleagues were contaminated by other body fluids especially cervical mucus—a rich source of the enzyme glucuronidase, and, in fact, if catheter specimens were used it was found that oestriol was largely excreted in the conjugated form right up until delivery. If we add his conjugated and free figures for oestriol together we obtain the graph (Fig. 9) which shows the excretion of oestriol throughout pregnancy and one which, we shall see shortly, is remarkably similar to those which have been obtained in recent years by the use of improved chemical methods.

At this point we would like to recall to you that in 1934 another classical paper had been published in the *American Journal of Physiology* by George and Olive Smith. This paper was entitled "Excessive gonad-stimulating hormone and subnormal amounts of estriol in the toxemias of late pregnancy" and was one of the first of a long series of distinguished communications on this subject that these authors were to make. We are sure that many present will scarcely realize that this fundamental contribution was made almost a quarter of a century ago.

Excretion of Oestriol in Normal Pregnancy Urine (Edinburgh Studies)

Brown (1956) published the details of his method of measuring oestradiol, oestrone and oestriol in the urine and in the following year was able to demonstrate the application of his method to the urinary oestrogen excretion in normal pregnancy. He showed that the three oestrogens increased from the luteal phase of the cycle of conception until term when they fell rapidly. Oestriol excretion increased a thousandfold and oestrone and oestradiol thirtyfold from the 10th week.

Since 1956 we have been able to add a further ten normal pregnancies to his series and the following graph (Fig. 8), which we can refer to as the "Edinburgh oestriol excretion curve", is based on three hundred and nine observations on 14 normal pregnancies. As far as possible, weekly 24-hour urinary collections were obtained from the 9th to the 41st week of pregnancy. Figure 7 shows the mean oestriol curve

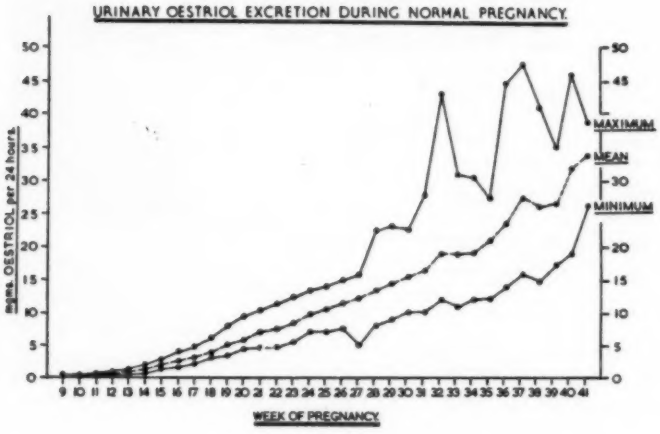

FIG. 8

Urinary oestriol excretion during normal pregnancy. Shows maximum, mean and minimum at each week of pregnancy in 14 normal pregnancies.

throughout pregnancy and it will be seen that there is a reasonably smooth rise in oestriol excretion from the early weeks until 40 weeks when approximately 31·5 mg. of oestriol are being excreted daily. When we look at Figure 8 on which the maximum, mean and minimum amounts of oestriol excreted each week are plotted, we see that there is a wide scatter of results which naturally becomes more obvious as we enter the third trimester of pregnancy. It will be clear that it will be only in the exceptional case that a single reading can have much significance. A similar wide scatter of results is noted in pregnanediol excretion in normal pregnancy. The significance is not clear as it is neither due to errors in urine collection nor to mistakes in chemical methodology.

Lenters in 1958 reported the results of his studies on oestriol excretion in normal and abnormal pregnancy, and we are all delighted that this afternoon Professor ten Berge is here to tell us something of this work. The method that Lenters used to measure oestriol was different from Brown's, depending on fluorimetry rather than on colorimetry. Figure 9 shows the Edinburgh and the Lenters oestriol curves, and it will be noted that although the two curves end at a very similar point at the 40th week of pregnancy, there is a discrepancy of several milligrams during several of the rather vital weeks of the third trimester. The chemists will have to tell us the reasons for this but it will be clear that we cannot directly compare results obtained by Brown's method with those of Lenters.

For historical interest we have included the Marrian curve of 1935 (Fig. 9). The oestriol levels are much lower throughout pregnancy but the curve makes a brave spurt towards term and is not much lower than the more recent figures.

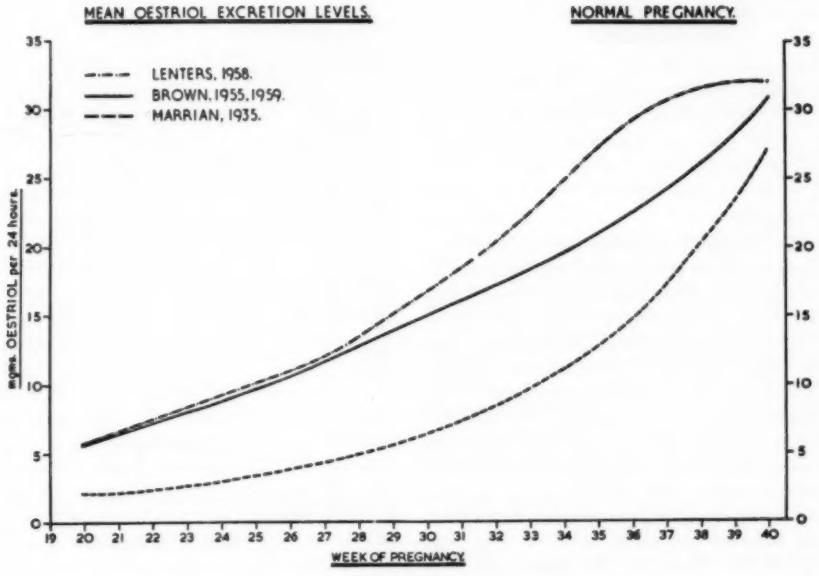

FIG. 9

Mean urinary oestriol excretion levels obtained by Lenters, Brown and Marrian.

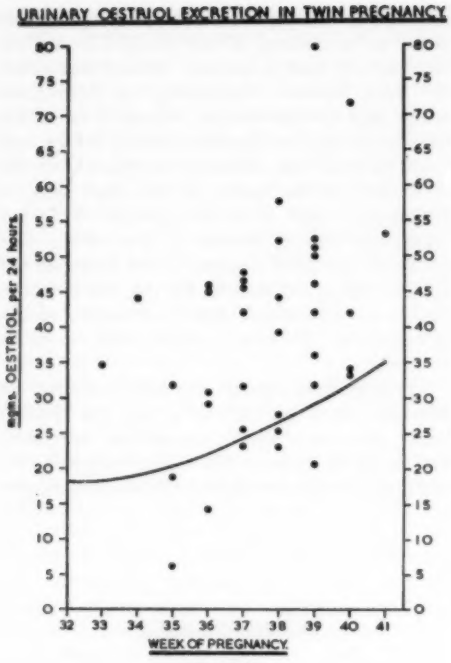

FIG. 10

Urinary oestriol excretion in twin pregnancy. Thirty-eight readings obtained from 12 patients.

Twin Pregnancy

We were fortunate in being able to obtain a fair sample of twin pregnancies and Figure 10 shows some thirty-eight readings obtained from 12 patients. It is, of course, very difficult to obtain strictly normal twin pregnancies and some of these patients showed some oedema and one or two a modest hypertension. This graph shows that on the whole the oestriol excretion in twin pregnancy is greater than the single series. If oestriol excretion is a function of placental weight, then this increased oestriol excretion could have been expected. The highest recorded oestriol excretion of 79·6 mg. was obtained at the 39th week of pregnancy in a binovular twin pregnancy delivered at the 40th week, the placentae weighing 3 pounds. It is doubtful, however, whether these higher figures are statistically significant.

Oestrogen Excretion in Pregnancy Toxaemia

The clinician still awaits some means of estimating placental function preferably by some fairly simple chemical method such as the measurement of a steroid metabolite. That there may be a reduction in oestriol excretion in certain cases of hypertensive toxaemia is undoubtedly true. We have not ourselves made any special study of this problem but in 12 patients with pre-eclampsia, who were under study for other purposes, we obtained the following results (Fig. 11). A fairly wide scatter of oestriol excretion rates is noted. Three patients who had excretion rates of less than 10 mg. daily after the 38th week, were delivered of babies under 5½ pounds.

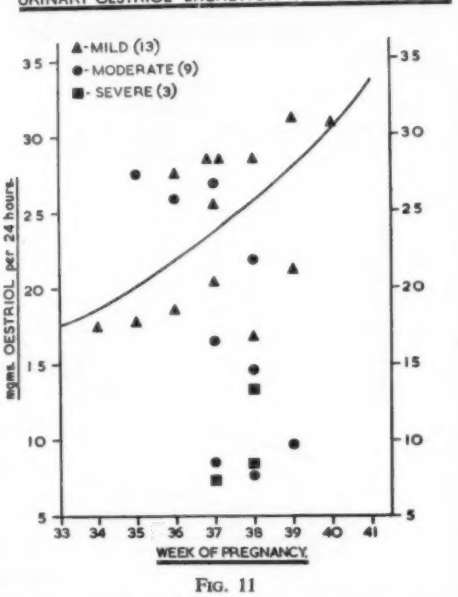

FIG. 11

Urinary oestriol excretion. Values obtained in 12 patients with varying degrees of pre-eclampsia.

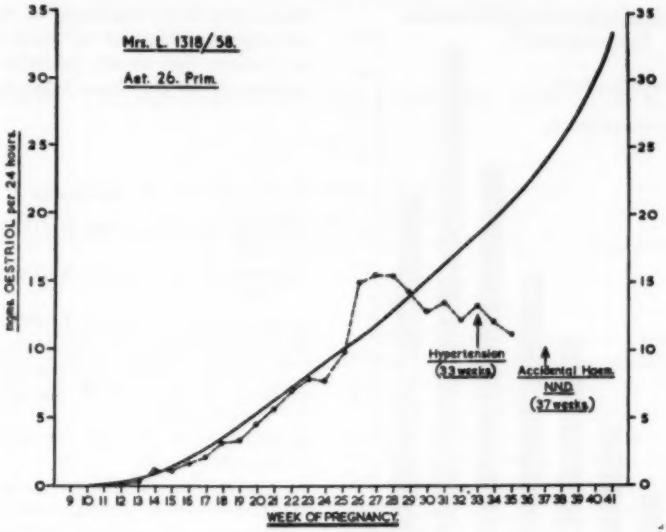

FIG. 12

Urinary oestriol excretion levels in a patient who developed pre-eclampsia and accidental haemorrhage.

Figure 12 shows the oestriol excretion curve of a patient who was originally included in the normal series at the beginning of her pregnancy. It will be seen that there is a falling oestriol excretion some little time before she developed pre-eclampsia at 33 weeks. She then had an accidental haemorrhage and delivered herself at the 37th week of a 5 pounds 9¼ ounces baby which died after a few hours.

We look forward to hearing the results of the work carried out in Professor ten Berge's department on this important subject.

The Blood Oestrogens in Pregnancy

Miss Roy and Dr. Brown (1959) have developed a colorimetric method for estimating the blood oestrogens (Oestradiol, Oestrone and Oestriol) in pregnancy. At present we are following a group of some 15 women through normal pregnancy and Figure 13 shows our results to date. There is a wide variation in the values of total oestrogens obtained at each month but the mean makes steady progress. The latter weeks of pregnancy have had to be filled in with "random" patients and the results should be accepted with caution. The fall in blood oestrogen in the last four weeks may be valid, and we believe that this phenomenon is noted in blood progesterone levels in human pregnancy.

We have had the opportunity of measuring the blood oestrogens in some 16 patients suffering from pre-eclampsia between the 30th–41st weeks of pregnancy. The results show a wide variation but it may be noted that although most of the values obtained were lower than the normal yet the highest blood oestrogen value we have obtained in any pregnant woman was 30·5 μg. per 100 ml. from a patient with severe pre-eclampsia with a normal urinary output.

CONCLUSIONS

Most of our remarks this afternoon have been of a factual nature and in the short time at our disposal we have avoided theorizing. We are

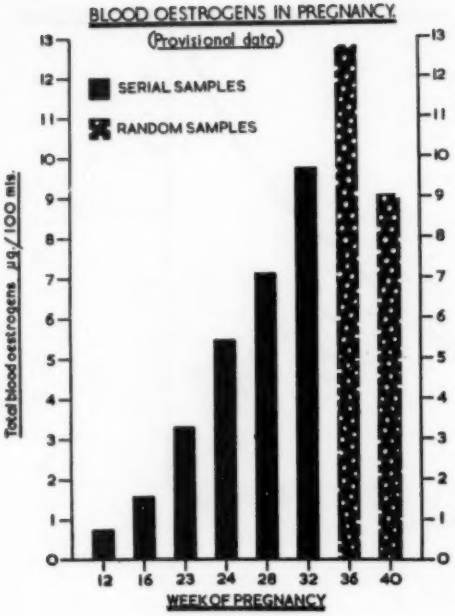

FIG. 13

Blood oestrogens (Oestradiol, Oestrone and Oestriol) in pregnancy. Serial follow-up to the 32nd week obtained from 15 normal pregnant women. Values at 36th and 40th weeks obtained from random samples.

really only at the beginning of our knowledge of oestrogen metabolism in health and disease, yet we believe that steady progress in the clinical application of our knowledge is being made.

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OESTROGEN THERAPEUTICS: METABOLIC CONSIDERATIONS

BY

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ALTHOUGH the oestrogens were originally regarded as water-insoluble substances, which had to be administered parenterally in oily solution, it later became clear that chemical modifications could alter their metabolism so as to augment their potency, or make them active when administered by mouth. The discovery of synthetic oestrogens by Dodds and his colleagues opened up an entirely new vista for research in oestrogen therapeutics, the exploration of which still continues.

One of the earliest relevant observations was that oestradiol, the most potent natural oestrogen, had only a very evanescent effect when injected intramuscularly but if it were esterified, as the benzoate or dipropionate, its potency was greatly augmented and the effect of a single injection was noticeably prolonged. It is generally agreed that the effect of esterification is to delay the absorption of the oestrogen, which otherwise is rapidly absorbed and equally rapidly inactivated by the liver. The search for other methods of delaying absorption, so as to prolong oestrogenic action, led to pellet implantation, the use of microcrystalline suspensions of oestradiol benzoate ("crystules") and to other long-acting esters, such as oestradiol valerianate (primogyn-depot). The chief objections to pellet implantation are that it is less simple to carry out than ordinary injections and that the effect is apt to be too long-lasting—a 50 mg. pellet of oestradiol may remain active for a year or more. A 10 mg. injection of oestradiol benzoate microcrystals or of oestradiol valerianate produces an effect lasting about 3 weeks; the valerianate, being in solution, is easier to handle than the suspension of microcrystals.

Although oestrone is weakly active by mouth, it has never had much therapeutic use, mainly because of the introduction by Dodds in 1938 of stilboestrol, which is about 25 times more potent and, of course, very much cheaper. The liability of stilboestrol, in doses above 1 mg. per day, to produce unpleasant side effects, especially nausea, vomiting, abdominal discomfort, headache and bloating (experienced by about 20 per cent of patients—but not by pregnant women) led to the search for other oral oestrogens free from this drawback. Hexoestrol and dienoestrol were introduced as less toxic oestrogens but, as they are also appreciably less potent than stilboestrol (hexoestrol about 1/20th and dienoestrol a quarter) there is little doubt that, in physiologically equivalent dosage, they are no less toxic than stilboestrol. The same is probably also true for the semi-synthetic oestrogen ethinyloestradiol, the most potent oral oestrogen known, about twenty-five times as active as stilboestrol. The preparation of "conjugated equine oestrogens", marketed as premarin, of which oestrone sulphate is probably the principal ingredient, is of value in that it is singularly free from the side-effects of other oral oestrogens. A 1·25 mg. tablet of premarin is equivalent to about 0·5 mg. of stilboestrol.

The cause of the side-effects of oral oestrogens is quite unknown. It does not appear to be due to a direct action on the stomach since if enteric-coated stilboestrol tablets are given to patients who have suffered nausea from ordinary stilboestrol, they experience the same effects but coming on about four hours later. Parenteral oestrogens never seem to produce these side

effects. In pregnancy, the tolerance for oral oestrogens increases enormously. Such are the facts, but no adequate explanation for them is forthcoming.

Little is known about the metabolism of synthetic oestrogens; in fact, for the most part they appear to undergo no metabolic transformation and to be excreted unchanged. This may, in part at least, account for the high oral potency of these substances.

Another synthetic oestrogen, methallenoestril (vallestril), a member of the allenolic acid series, is a weak oral oestrogen (its potency is about 1/25th that of stilboestrol) which is said to have little or no action on the endometrium. For this reason, it has been advocated in the treatment of the climacteric syndrome because it is unlikely to cause uterine bleeding. Freedom from toxic effects is also claimed for it, but, in evaluating this, its low potency has to be taken into account. Indeed, the case that it behaves differently from any other weak, oral oestrogens has not been convincingly established.

Prolongation of action on oral administration is achieved by the synthetic oestrogen chlorotrianisene (TACE). This substance is in fact a pro-oestrogen—that is, a compound which is not itself oestrogenic, but is converted in the body into an active oestrogen. This distinction between oestrogens and pro-oestrogens is readily made on the basis of the vaginal response in oöphorectomized mice; the former are effective by local application or by injection, but the latter are ineffective on local application though they produce the characteristic cornification on injection. The site of conversion is not known for certain but is suspected as being the liver. Chlorotrianisene is apparently stored in body fat, from which it is slowly released, to be converted into the actively oestrogenic form. In consequence, if daily treatment is given for a month, the effect persists for some weeks afterwards and declines slowly. Since, in the oestrogen treatment of the climacteric syndrome, the aim is to replace a rapidly declining oestrogen level by a more slowly declining one, chlorotrianisene would appear to be well suited for the purpose. The manufacturers claim that following a single course of treatment with 2 capsules (each containing 12 mg. of chlorotrianisene) daily for 30 or 60 days, 50 per cent of climacteric patients do not require further treatment, while of the remainder relatively few will need more than one similar course. My own experiences with this substance confirm its effectiveness, but have not substantiated its "once and for all" curative efficacy. A further claim, that uterine bleeding does not occur following its use, also cannot be substantiated.

Local therapy with oestrogens has been advocated in a number of conditions where either intense local oestrogenic stimulation, or where moderate local action without systemic effects, is desired. An example of the former is utero-cervical hypoplasia which may show a quite remarkable response to the injection of oestrogen in oily solutions into the substance of the cervix. Recent personal experience with oestradiol valerianate in promoting utero-cervical growth has been most encouraging. Injections of 10 mg. have been made at weekly intervals (the cervix is extraordinarily tough and pushing a hollow needle into its substance requires an appreciable amount of force); evidence of growth is usually seen even at the time of the second injection, and 3 injections have often been all that was needed.

Other applications of local oestrogen therapy have been for vaginitis, either senile or prepuberal, and to promote mammary growth. For the former, stilboestrol pessaries of 0·5 mg. or less daily will promote rapid vaginal cornification with little risk of undesirable systemic effects—especially uterine bleeding. For the latter, oestrogens of various kinds and in varying dosages have been inuncted into the breasts in ointments, mostly of the vanishing cream variety. Success is unlikely in women who have normal ovarian function, with regular menstruation; in these, the mammary hypoplasia is usually due to deficiency of mammary tissue and particularly of interlobular fat, so that response to oestrogen is out of the question. Where the mammary hypoplasia is associated with ovarian insufficiency, systemic oestrogen therapy is preferable to its local application.

OESTRIOL ASSAYS IN THE TREATMENT OF TOXAEMIA

BY

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THE high foetal mortality in toxaemia of pregnancy is due to placental degeneration. The reason for this may be a decrease in uterine circulation whereby less blood is transported to the intervillous lake, but it is not only the condition of the arteries in the uterine wall which defines the flow of maternal blood in the intervillous spaces. The capillary action of the villi is also of great importance.

By the action of the precapillaries, the capillaries of the villi are filled intermittently. The small spaces between the villi are narrowed and widened more or less regularly, exerting a pump mechanism whereby blood is drawn up into the placental bed. An autonomic action of the precapillaries in the villi was observed by us and demonstrated on a film which was shown at your last Congress.

With toxaemia the circulation rate is decreased by perhaps one-third of the normal value, but this may not be entirely due to narrowing of the arteries in the uterine wall. In our opinion pathological changes in the placenta are also significant. In toxaemia, fibrin accumulates in the intervillous spaces, villi fuse together and become oedematous, thrombi collect in the smaller blood vessels, the chorionic epithelium undergoes degeneration, necrotic villi appear, fibroplastin is liberated and fibrin accumulation is thereby enhanced. The most marked changes take place during the terminal weeks. Foetal growth is impaired or foetal death occurs. Dr. Pollak in our laboratory counted the degenerated villi in the placentae of toxaemic patients and found a correlation between foetal weight and the number of degenerated villi.

The degree of placental degeneration may be assessed by carrying out serial estimations of oestriol excretion in 24-hours urine, and these assays may be of clinical value in determining the most suitable time for inducing labour. In former years using clinical rules the results of induction were often unsatisfactory. During the last 3 years, 1956–1958, we have carried out oestriol estimations in 104 patients with severe toxaemia out of a total of 294 cases of toxaemia, but even with oestriol assays it may be difficult to decide the optimum time for induction. As the Table shows, 27 of the 294 infants were lost, an overall wastage of 9 per cent. In the oestriol group of 104 women with severe toxaemia, the foetal loss was 14 (14 per cent); allowing for 2 infants with malformations and 1 hydropic foetus, the corrected foetal mortality in this group was 11 (10 per cent). Of these 11 infants who failed to survive, 3 died *in utero* before the 34th week, 1 case was admitted too late, and in 7 induction was performed too late.

TABLE I

Results of Treatment of Toxaemia with Induction of Labour on Serial Oestriol Indication, 1956–1958
(Percentages in brackets)

Total number of patients with toxaemia ..			294	
Total perinatal foetal mortality			27	(9)
Patients with more than 2 oestriol assays (severe toxaemia)			104	
Perinatal foetal mortality			14	(14)
Malformation	2			
Hydrops	1			
Toxaemia alone ..	11	(10)		
Died *in utero* before 34th week			3	
Admitted too late			1	
Induced too late			7	(7)

The following information was learned during

those years. Values below 10,000 gamma with our method indicate a real danger to foetal life. It is a bad sign when oestriol values do not rise in the last trimester. With values below 10,000 gamma, preference should be given to Caesarean section as a means of delivery. With levels around 15,000 gamma delivery *per vaginam* may be permitted in favourable circumstances. We found that just before foetal death diminished oestriol excretion occurred. However, daily oestriol values fluctuate and a fall should be judged by at least 2 estimations. With intrauterine death, oestriol values fall abruptly to very low levels, a phenomenon we observed in 12 cases. In some of the cases with a dead foetus, the placental bed could not be detected by a scintillation counter after the intravenous injection of radioactive iodinated human serum-albumin. This is also an argument for the role of the foetal precapillaries in the placental villi for the maintenance of the blood flow in the intervillous lake.

Statistical studies demonstrated a correlation between clinical features, macroscopical and microscopical appearances of the placenta, foetal weight and urinary oestriol excretion.

Professor ten Berge also presented a short film demonstrating capillary action in the placenta.

DISCUSSION ON OESTROGEN METABOLISM

DR. R. V. SHORT (Cambridge)

I MUST apologize at the onset in that what I shall be discussing has no direct clinical application and I am afraid I shall be touching rather more on the veterinary than on the human aspect. My talk is really about the synthesis of oestrogens in the ovary. We have heard already this afternoon about the metabolism of the naturally-occurring oestrogens and the metabolites found in the urine. Now I should like to turn your attention for a few moments to the biologically active oestrogens themselves as secreted by the ovary and to the way in which the ovary synthesizes them.

Our present knowledge of the bio-synthesis of oestrogens by the ovary can roughly be summarized as follows: there is fairly good evidence that progesterone is converted into 17 hydroxy-progesterone and then the side chain is split off to give an androgen, androstenedione; testosterone may also be formed at this stage, though there is no very definite evidence of that. This 17-ketosteroid, this androgen—be it androstenedione or testosterone—is converted to oestrone and then on to oestradiol. That is the present status of our knowledge as to how oestrogens come to be formed in the follicular fluid. I should like you to notice that in the formation of an oestrogen the process must go through progesterone and through an androgen as intermediates on the pathway.

I should like to describe to you now a small-scale experiment which I have carried out on the analysis of steroids in follicular fluid. For this purpose I have reverted to the mare, as many endocrinologists have done in the past, because the mare is peculiar in that the ovaries are very large and contain a large quantity of follicular fluid. In some cases I have been able to obtain well over 100 ml. of follicular fluid from a pair of ovaries. In this way it has been possible to obtain very easily many litres of follicular fluid—an advantage which perhaps you as clinicians may not have! I have applied to this follicular fluid a sort of omnibus extraction procedure which is not very elegant but it does enable one to obtain a very wide spectrum of the steroids that are present. Using chromatography, one can identify progesterone, androstenedione, testosterone, oestrone, oestriol and oestradiol. There are also other steroids not as yet characterized.

When I started on this work about a year ago, oestriol had never actually been isolated from the mare at all, neither in urine nor tissues but it seems as if I have been finding it in follicular fluid. I have also been trying to identify these other compounds, and in this we have been fairly successful (Table I). A very surprising finding was the discovery of cortisol (hydrocortisone) in follicular fluid. I think that must almost certainly be a reflection of the level of cortisol in the peripheral blood when it happens to diffuse through into the follicular fluid. Then there is progesterone in considerable amount—(62 micrograms); 17-alpha-hydroxy-progesterone in fair quantity (the next intermediate in this little pathway of bio-synthesis); androstenedione—quite a potent androgen and incidentally the main androgen produced by the human adrenal—again in appreciable amounts; and then a strange finding—cis-testosterone (that is to say testosterone with the hydroxyl group not in the conventional position)

TABLE I

Steroids in 100 ml. of Mare Follicular Fluid

Steroid	Micrograms
Cortisol	6
Progesterone	62
17 alpha-Hydroxyprogesterone	33
Androstenedione	68
cis-Testosterone	12
Unknown	26
Oestrone	37
Oestradiol 17-beta	300
New oestrogen	68

which is not a very active androgen; next another steroid which we have been completely unable to identify so far—we know that it is a 17-ketosteroid and it is probably an intermediate in the synthesis of oestrogens from these androgens; then, oestrone—not very much; oestradiol 17-beta in tremendous amount—300 micrograms; (no oestradiol 17-alpha although it is a common urinary metabolite); and, finally, perhaps the most interesting finding of all—a completely new oestrogen which has not been isolated from human urine. We are not completely certain of its identity yet; we know that it behaves very like oestriol but it is definitely not oestriol. We hope within the next week or so to have it characterized completely.

I should like to conclude by throwing out two rather controversial ideas. We have seen this pathway of bio-synthesis in the ovary and we see that the ovary produces androgens as an intermediate to the production of oestrogens. I think it is possible that the difference between the ovary and the testis is just that the ovary is slightly more specialized; it has one more set of enzyme systems which can carry these androgens on and form oestrogens with them—the testis cannot do this quite so efficiently. The difference between the corpus luteum and Graafian follicle is probably that the luteal tissue enzymatically is less specialized so that it cannot carry on from progesterone to oestrogen nearly so well as the cells lining the follicle. We are now working on some cases of virilizing ovarian cysts in cattle trying to see if this can be borne out in practice, whether in fact one can get virilism due to the inability of the ovary to carry out this final bio-synthesis from the androgen intermediates right through to the oestrogens.

PROFESSOR J. H. M. PINKERTON (London)

OESTROGEN PRODUCTION IN THE IMMATURE HUMAN OVARY

(OBSERVATIONS BASED UPON HISTOCHEMICAL STUDIES)

STEROID hormone production in the theca cells of the ovary, as in the testes (Dempsey, 1948), adrenal (Elftman, 1947) and placenta (Hertig, 1958), is associated with concomitant alkaline phosphatase activity. In the adult ovary such activity is scarcely evident in the theca before an antrum appears and at this stage oestrogen production is low. After formation of the antrum, as the follicle grows larger, alkaline phosphatase activity increases in the theca interna, and oestrogen production gradually rises (McKay and Robinson, 1947; Pinkerton and McKay, 1957).

While the biochemical significance of this association in theca interna cells of alkaline phosphatase and oestrogen production is not yet understood, there is no doubt that such an association constantly exists. The presence of alkaline phosphatase activity in the theca interna cells of a follicle may therefore be regarded as evidence that the follicle is being stimulated and as a result is producing oestrogen. Study of the alkaline phosphatase reaction in the follicles of the immature ovary might be expected to throw some light on the functioning and regulation of the developing ovary.

MATERIALS AND METHODS

The material, which is part of a larger collection used for a study of the human ovary

TABLE I

Ages of the Ovaries Studied

	Foetal				Children's Ovaries												
	Age (Weeks)				Age (Years)												
	20	28	36	40	2/12	4½/12	9/12	1 3/12	3	3 4/12	3 11/12	4 5/12	7 9/12	7 11/12	9 8/12	14 9/12	Total
No.	5	1	1	2	1	1	1	1	2	1	2	1	1	1	1	1	23

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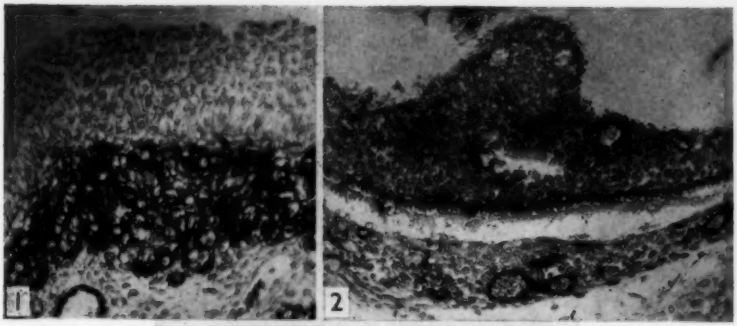

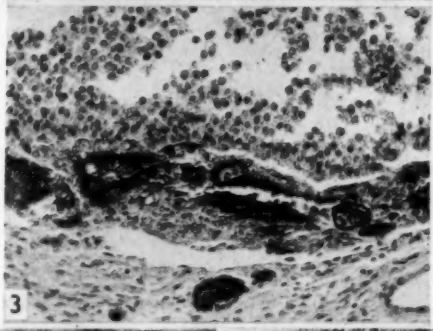

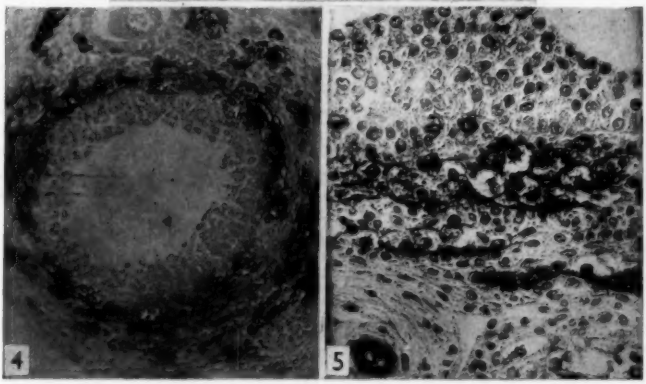

FIG. 1. Adult. Wall of mature follicle from an adult ovary. The liquor folliculi and the granulosa show no alkaline phosphatase activity. The partially luteinized theca interna cells react strongly around the periphery of their cytoplasm. The intima of the large thecal blood vessels also reacts. Alkaline Phosphatase. ×125 approx.

FIG. 2. 3 years 1 month old. Wall of a moderate sized Graafian follicle near the cumulus. Alkaline phosphatase activity is present in the intima of the thecal blood vessels, but not in the theca cells. Alkaline Phosphatase. ×150 approx.

FIG. 3. 14 years 9 months old. The wall of a moderate-sized Graafian follicle showing well marked alkaline phosphatase activity in the luteinized theca cells. Alkaline Phosphatase. ×150 approx.

FIG. 4. 314 mm. foetus, about 36 weeks. Small Graafian follicle. The theca cells are luteinized and show well-marked alkaline phosphatase activity. Alkaline Phosphatase. ×150 approx.

FIG. 5. 2 months old infant. Large Graafian follicle. Some of the theca cells are luteinized and show a marked alkaline phosphatase reaction. Alkaline Phosphatase. ×300 approx.

throughout its life span, comprises 23 pairs of ovaries at progressive stages of development from the 20th week of intra-uterine life until the 14th year (Table I). The tissue was fixed in cold absolute acetone as soon after death as possible, and subsequently sectioned and reacted for alkaline phosphatase using Seligman's technique. Other sections were stained with haematoxylin and eosin; and by McManus' periodic Schiff method for glycogen and glycoproteins.

Observations

Follicular oestrogen production reaches a peak just before ovulation and the alkaline phosphatase activity in the theca of the largest follicles (diameter about 10 mm.) is greatest at this time (Fig. 1).

The ovaries of children between the ages of approximately 1 year and 9 years present a different appearance. Follicles at all stages of development and atresia are constantly present, but the Graafian follicles are small, the largest being about 2 mm. in diameter. Little or no alkaline phosphatase activity is present in the theca interna of these ovaries (Fig. 2). This suggests that, while there is sufficient follicle stimulating hormone (F.S.H.) acting on the ovaries to produce antra in some follicles, the concentration is not high enough to cause oestrogen production at this stage of the child's development.

After the age of 9 years, before the onset of ovulation, a marked change appears in the follicles. They increase in size up to a diameter, in some ovaries, of 10 mm., and alkaline phosphatase activity appears in the luteinized theca interna cells in concentrations approaching that of adult follicles (Fig. 3).

These follicles are apparently responding to the increased output of F.S.H. which is known to occur in the years immediately preceding the menarche (Bahn *et al.*, 1953; Nathanson *et al.*, 1941) so that the theca cells are now producing oestrogen, the breakdown products of which are demonstrable, for the first time since birth, in the urine at this age (Jayle and Crepy, 1952).

While there is little or no sign of alkaline phosphatase activity during childhood until about 9 years of age, the ovaries obtained in late foetal life and early infancy show definite evidence of activity in the theca around any follicle which has developed to the antral stage whether large or small.

A Graafian follicle is first seen in this material in a 36-week foetus. It is small but the theca is well luteinized and there is a strong alkaline phosphatase reaction in its cells and blood vessels (Fig. 4). This is characteristic of all the Graafian follicles seen in the ovaries from foetuses and children in the first few months of life (Fig. 5).

It is clear, therefore, that the follicles of the human ovary are capable of responding to adequate stimulation at any time from the 36th week of foetal life onwards. There is nothing in the histological and histochemical features of this material to suggest that ovarian development at puberty is due to a ripening process in the ovary which renders it sensitive to stimulation by gonadotrophins. It would seem rather that the pre-antrum follicles, even before birth, are capable of growth and oestrogen production if suitably stimulated, and that the marked development which precedes the menarche is due chiefly to the increasing concentrations of pituitary gonadotrophins which occur at this time.

The nature of the stimulating substances which produce the follicular development sometimes seen towards the end of foetal life is not known. Such evidence as is available would suggest that the follicles are stimulated by chorionic gonadotrophins acting in conjunction with maternal oestrogen, or F.S.H., or both (Penchartz, 1940; Williams, 1945).

Acknowledgments

This work was begun during the tenure of a Rockefeller Research Fellowship at the laboratories of Dr. A. T. Hertig at Harvard Medical School and of Dr. D. G. McKay at the Free Hospital for Women, Brookline, Massachusetts, U.S.A.; I am indebted to them both; and also to Miss Eleanor Adams, B.Sc., and Miss Sarah Danziger for technical assistance, and Dr. John Craig, Pathologist of the Children's Hospital, Boston, Massachusetts, U.S.A., who supplied most of the infant ovaries.

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Dr. Arnold Klopper (Aberdeen)

The Effect of Oestriol on Plasma Water Content

In Aberdeen we have been considering another aspect of oestrogen metabolism which has some bearing on the data Dr. Brown and Professor Kellar have been presenting. Professor Kellar has already remarked on the fact that the output of oestriol in the urine increases several thousand-fold during pregnancy. We have been wondering about the purpose of this tremendous increase in oestrogen production. In the final analysis we have little more than histological generalizations about the role of oestrogen in the body.

It has been suggested that oestrogens play a part in water balance and distribution in the body. Dr. Paaby of Aalborg and I have been pursuing this line using a technique elaborated by him in Denmark. In short this consists of taking a sample of blood from a resting starved patient under rigidly controlled basal conditions. The water content of the plasma is then estimated by drying the plasma to a constant weight. We have also measured the total water present in the body by the dilution of heavy water and oestriol by the Brown method. By these means we have followed the changes in plasma water during pregnancy and the normal

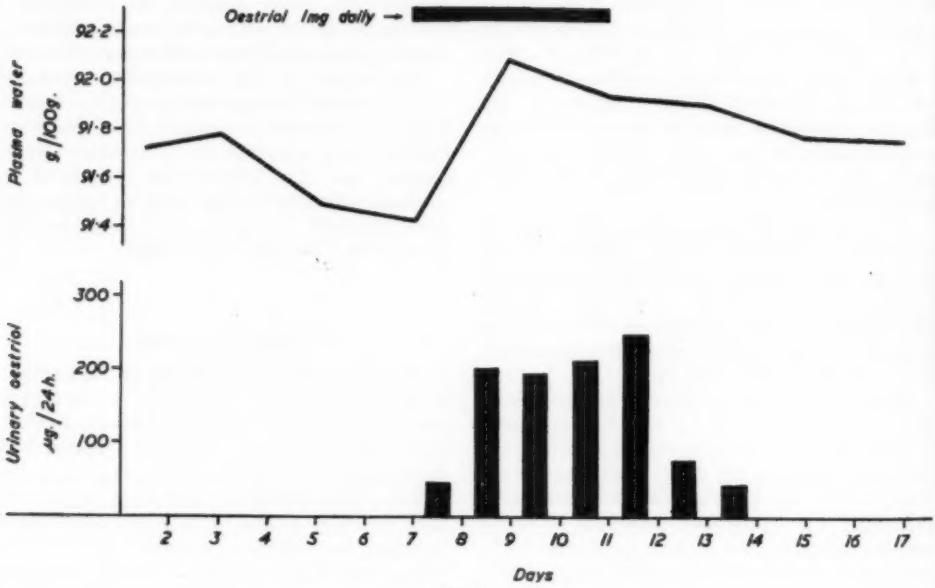


Fig. 1

The effect of oestriol on the water content of plasma.

cycle. Changes in plasma water follow alterations of oestriol excretion so closely as to suggest very strongly that they are part of the same process. Figure 1 shows the sort of result obtained when oestriol is administered to a post-menopausal woman.

We first measured the plasma water while she was excreting the relatively tiny amounts of endogenous oestriol characteristic of the post-menopausal state. Then we gave her 1 mg. of oestriol daily by mouth for 4 days. Of course her urinary output of oestriol increased very sharply. This was followed shortly by a marked rise in the percentage of water in the plasma which declined slowly to previous levels after stopping the oestriol. Before oestrogen administration her total body water was 25·41, after 3 days of oestriol administration it rose to 30·51 and a week later had fallen to 29·31. Apparently, therefore, the oestrogen administration resulted in a massive retention of water. Most of this was probably interstitial water but some has appeared in the plasma to cause the relative haemodilution here recorded.

Oestriol Excretion in Late Pregnancy

I have some data on oestrogen excretion from Aberdeen which has a bearing on what Professor ten Berge has been saying. Earlier writings on oestrogen excretion make great play with the considerable natural variation to be found in urinary oestriol. It seemed important to know how much this large scatter in the results would be reduced by present-day techniques. We set out to find just how much difference in oestriol excretion would occur from day to day in the same patient and from patient to patient when the assays were done by a modification of the Brown process.

To this end we selected six normal primigravidae at 38 weeks and admitted them to a research unit for six days each. They were not confined to bed, but in view of the fact that they were in a metabolic unit where there were no chains to pull, it is eminently probable that correct 24-hour urines were collected. We tried to standardize conditions as rigidly as possible. Their fluid intake was strictly controlled on a pattern of high, normal and restricted intake according to a statistical lattice. The day-by-day oestriol output in these six primigravidae showed a very considerable scatter.

The mean excretion in this group was 32·04 mg. which corresponds almost exactly to the mean values recorded by Professor ten Berge in Groningen, Dr. Brown in Edinburgh and Dr. Ittrich in Berlin by different methods. It seems very likely that we are measuring much the same thing.

The day-to-day variation in the same patient shows a standard deviation of 8·81 mg. about the mean, which gives a coefficient of variation of 27·5 per cent.

The estimate of variation between one patient and another is 9·63 mg., giving a coefficient of variation of 30 per cent. It follows that the patient to patient variation is quite considerable and that cross-sectional studies involving single observations on individuals will require very large numbers of cases to give valid conclusions. It would appear to be more economical to do serial studies on smaller numbers.

These figures suggest a note of caution in the conclusions to be drawn about the use of urinary oestriol assay as a measure of placental function. Single observations are subject to so much individual variation that only rarely are values encountered which can with confidence be called abnormal and then they are liable to occur in severely affected cases where a sphygmomanometer or a foetal stethoscope will give the answer more directly. Serial observations are more reliable but take so long as to be of little use in the day-to-day management of the individual patient.

Professor C. Scott Russell (Sheffield)

An Estimate of Some of the Errors of Assaying Urinary Oestradiol, Oestrone, and Oestriol (Using Brown's Method)

I also wish to speak about the errors of assay because before any biochemical assay is used in clinical practice it is important to know how much reliance can be placed on it. Dr. Pamela Wray, M.D., M.R.C.O.G., working in my

TABLE I

Oestriol Excretion in mg. per 24 Hours. Duplicate Readings on Consecutive Days

Patient	Day 1		Day 2		Day 3		Totals
A	39·6	35·8	46·1	43·6	34·2	32·0	231·3
B	22·7	26·2	23·0	24·1	17·4	17·2	130·6
C	39·2	46·2	50·0	44·8	27·6	25·4	233·2
D	22·4	24·8	24·8	25·0	22·4	27·0	146·4
E	22·7	30·8	32·2	34·2	29·1	29·6	178·6
F	48·7	49·2	43·2	41·5	47·9	49·2	279·7
G	30·2	32·5	27·9	28·8	34·2	32·0	185·6
H	30·7	32·2	33·6	34·6	33·9	32·8	197·8
I	38·1	40·6	33·9	35·2	37·0	37·5	222·3
J	49·2	46·8	40·2	30·8	42·4	45·4	254·8
Totals	708·6		697·5		654·2		

TABLE II

Oestrone Excretion in μg. per 24 Hours. Duplicate Readings on Consecutive Days

Patient	Day 1		Day 2		Day 3		Totals
A	2,436	2,576	3,000	2,835	2,736	2,560	16,143
B	1,904	1,832	2,220	2,208	1,560	1,764	11,488
C	2,100	2,060	2,080	2,020	1,810	1,550	11,620
D	610	690	600	630	620	520	3,670
E	2,310	2,576	3,304	3,360	3,008	2,904	17,462
F	1,128	1,148	968	838	1,140	1,244	6,466
G	392	398	476	476	652	744	3,138
H	670	400	630	560	505	495	3,260
I	1,320	1,340	1,770	1,760	2,620	2,710	11,520
J	1,740	1,566	1,128	1,572	1,686	1,722	9,414
Totals	29,196		32,435		32,550		

TABLE III

Oestradiol Excretion in μg. per 24 Hours. Duplicate Readings on Consecutive Days

Patient	Day 1		Day 2		Day 3		Totals
A	238	274	145	150	300	308	1,415
B	524	552	412	416	586	608	3,098
C	710	770	800	800	820	700	4,600
D	450	520	240	290	570	580	2,650
E	200	204	360	376	208	220	1,568
F	216	176	392	412	368	372	1,936
G	120	130	40	52	176	184	702
H	196	108	308	272	300	300	1,484
I	1,140	1,150	730	690	410	430	4,550
J	544	504	348	468	410	330	2,604
Totals	8,726		7,701		8,180		

TABLE IV

Variations of Duplicate Readings

Oestriol			Oestrone			Oestradiol		
Mean	Standard Deviation	Coefficient of Variation	Mean	Standard Deviation	Coefficient of Variation	Mean	Standard Deviation	Coefficient of Variation
		(Per cent)			(Per cent)			(Per cent)
20	1·9	9·3	500	73	14·6	200	25	12·5
30	2·3	7·6	1,000	90	9·0	400	33	8·3
40	2·7	6·7	1,500	108	7·2	600	40	6·7
50	3·1	6·2	2,000	125	6·3			

department, has made a study of some of the errors of assaying the urinary oestrogens; she is not able to be here so I am reporting her results.

Ten intelligent women in the last month of a normal pregnancy collected 24-hour specimens of urine on each of three consecutive days. The content of oestriol, oestrone, and oestradiol 17β in each specimen was assayed by Brown's method. Duplicate assays were made. The total difference between the days was effectively random (Tables I, II and III). There was a considerable difference between duplicate readings, and examining this source of error it was found that the variation of the duplicate readings had standard deviations related to the mean size of the readings; the coefficient of variation for the error of duplicate readings ranged from 6 to 14 per cent (Table IV).

Besides the differences between the duplicate readings, there were great differences between patients. In addition there were serious in-

consistencies in the form of variation in the individual patients from day to day which accounted for a very substantial part of the error; for oestriol, the co-efficient of variation was 15 per cent; for oestrone, 19 per cent; and for oestradiol, 41 per cent (Table V).

TABLE V
Coefficient of Variation

Oestriol	15 per cent
Oestrone	19 per cent
Oestradiol	41 per cent
Pregnanediol	5 per cent

Clearly, the errors of assay are high, and the practical importance is that they must be taken into account when any attempt is made to interpret the meaning of variations in the reported levels of excretion. The assay of urinary oestrogens is being used to assist the management of abnormal pregnancy, so it is relevant to compare these estimates of error with those of pregnanediol (5 per cent), assay of which is also being used for much the same reason in pregnancy. Of course the difficulties consequent on the above errors can be reduced by examining more than one 24-hour urine specimen from each patient.

GUEST LECTURE

STUDIES IN THE CLINICAL AND BIOLOGICAL EVOLUTION OF ADENOCARCINOMA OF THE OVARY*

BY

HOWARD C. TAYLOR, JR., M.D.

Professor and Chairman

Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons and the Obstetrical and Gynecological Division (The Sloane Hospital) of the Presbyterian Hospital, New York, U.S.A.

INTRODUCTION

THE areas for which any medical discipline is responsible are difficult to define and are constantly changing. With the development of independent institutions for cancer research, it might perhaps be supposed that the obstetrician-gynaecologist should relinquish the non-clinical aspects of his oncology to the scientists more versed in the specialized techniques which now seem essential for the solution of so complex a problem as neoplastic disease.

Yet there are good reasons why we should not withdraw completely from this field. First, it is the clinician who knows the problem that needs to be solved, and partly through this knowledge, partly through the sense of urgency which his daily work engenders, may be able to supply a critical viewpoint and a special energy. It is further true that the worker in basic cancer research, seeking some simplification in an unbelievably difficult situation, tends to favour work with animal tumours. It is in the clinical departments that the results of such work must be tested for its validity in human tumours.

It was with these thoughts in mind that about five years ago a collaborative programme, depending on the co-ordinated efforts of investigators in several fields, was set up in the Department of Obstetrics and Gynecology at Columbia University for the study of the common malignant tumour of the ovary, the papillary serous cystadenocarcinoma. The original plan had been to concentrate on the problem of differentiation, or, as the clinician usually expresses it, the grades of malignancy, phenomena unusually well demonstrated in this particular neoplasm. As the work progressed we have followed a number of secondary lines of study and it seemed best to present this report on our work under the more general title selected.

FREQUENCY OF CARCINOMA OF THE OVARY

In 1956 cancer of the ovary ranked fifth in the United States as the cause of death from malignant disease among women, being surpassed in frequency only by cancer of the breast, uterus, intestine and stomach (Fig. 1). Figures on incidence collected in the State of New York (Randall and Gerhardt, 1954) indicated that during most of a woman's life the chance of her subsequently developing cancer of the ovary is about 1 in 100 (Table I).

TABLE I

Probability of Later Development of Cancer in Women of Indicated Ages in Percentages

Age	All Sites	Breast	Cervix	Endometrium	Ovary
20 ..	23·8	5·4	2·3	1·6	1·0
30 ..	23·7	5·4	2·3	1·6	1·0
40 ..	23·1	5·2	2·0	1·5	0·9
50 ..	24·5	4·6	1·6	1·4	0·8
60 ..	18·7	3·9	1·1	1·1	0·6
70 ..	14·9	3·0	0·7	0·7	0·4

Condensed from Table of Randall and Gerhardt.

* This investigation was supported in part by grants Nos. 215 and 413 from the Damon Runyon Memorial Fund, New York, N.Y., by research grant C-2428 from the National Cancer Institute of the National Institutes of Health, United States Public Health Service and by a grant from the American Cancer Society.

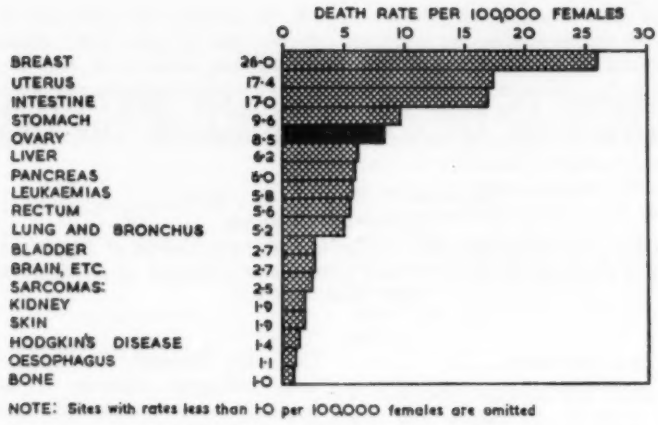


FIG. 1

Female cancer death rates by site. United States, 1956. Source: National Office of Vital Statistics.

Furthermore statistics collected over the years from 1930 to 1955 in the United States indicate a steady increase in the deaths from cancer of the ovary, from a rate of 4 per 100,000 in 1930 to 8 per 100,000 in 1955 (Fig. 2). This striking increase, evident even after corrections for the advancing age of the population, was occurring while the death rate from cancer of the uterus was steadily falling. That this increasing death rate from cancer of the ovary was not peculiar to the United States, but was occurring in Britain as well is also evident (Fig. 3). From these few figures it seems clear that carcinoma of the

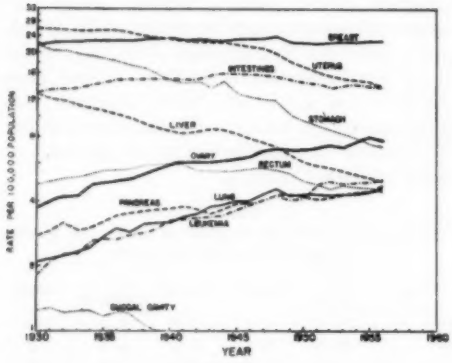


FIG. 2

White female cancer death rates by site. United States, 1930–1956. Rates for the white population standardized for age on the 1940 population of the United States. Sources of data: National Office of Vital Statistics and Bureau of the Census, United States.

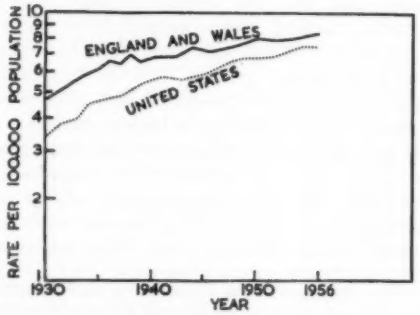


FIG. 3

Cancer of the ovary death rates. England and Wales and the United States, 1930–1956. Sources: United States National Office of Vital Statistics, and England and Wales Registrar General.

ovary is a problem to which more attention will have to be devoted.

Research on cancer of the ovary has taken a peculiarly academic form during the last decades, since it has been directed especially toward the rarer types. This has led to a sounder classification of the more exotic tumours and, as a by-product, has contributed to the knowledge of the embryology and the endocrinology of the ovary. It has left nearly untouched, however, the problem of the commonest ovarian cancer, the papillary serous cystadenocarcinoma.

In the series of 379 malignant ovarian tumours treated in the Department of Obstetrics and Gynecology at Columbia University, from 1922–1953, two-thirds were definitely of this type, and if, as appears justifiable, the undifferentiated cancers are added, the figure reaches three-quarters of the entire series (Table II). Finally,

TABLE II

Frequency of Types of Ovarian Cancer, 1922–1953

	No. of Cases	Per cent
Papillary serous cystadenocarcinoma	254	67·0
Undifferentiated adenocarcinoma (probably serous adenocarcinoma)	30	7·9
Papillary pseudomucinous cystadenocarcinoma	36	9·5
Granulosa cell carcinoma	24	6·3
Thecoma malignant	2	0·5
Dysgerminoma	6	1·6
Teratoma malignant	2	0·5
Unclassifiable	25	6·6
Total	379	99·9

if one considers not incidence but mortality this tumour accounts for nearly 90 per cent of the deaths attributed to cancer of the ovary.

It seems evident then that it is the papillary serous cystadenocarcinomas of the ovary to which we must devote our greatest efforts.

SPECIAL BIOLOGICAL FEATURES FOR STUDY IN SEROUS ADENOCARCINOMAS OF THE OVARY

The serous adenocarcinomas of the ovary present a number of special biological characteristics, which are not only of interest for this tumour itself, but offer promising opportunities for the study of neoplastic disease in general. Those that will be discussed are (*A*) histogenesis; (*B*) the development of a fluid phase of growth which seems to be the equivalent of the ascites tumour seen in some experimental animals; (*C*) the phenomenon of implantation and spontaneous regression; and finally, (*D*) the occurrence of histological subtypes, having demonstrably different grades of malignancy.

(*A*) HISTOGENESIS

(1) *Origin of Papilloma*

There seems substantial agreement that the papillary serous cystadenomas and cystadenocarcinomas arise from the layer of peritoneal cells overlying the cortex of the ovary (Goodall, 1920; Schiller, 1940; Kleitsman, 1951; Woodruff and Novak, 1954). This is the "germinal epithelium", so called because it was once thought to be the source of the ova. Actually this is "mesothelium" and, in a strict but remote embryological sense, these are mesotheliomas.

The belief in the peritoneal covering of the ovary as the source of these tumours depends largely on the convincing histological evidence of what seem to be the beginnings of cystadenomas in areas of ovary remote from the developed neoplasm and even in some otherwise normal ovaries with no tumour present. These changes appear first as simple epithelium-lined clefts (Fig. 4), which increase in complexity and cellular activity (Fig. 5) and eventually, with the deepening of adjacent clefts, seem to provide the origin for primitive, broad, connective tissue-rich papillomas (Fig. 6).

The ability of the serosa of the ovary to produce such structures seems to be shared, at times, by the contiguous peritoneal surfaces of the mesovarium, mesosalpinx and the tube itself, for occasionally vestigial papillary structures, sometimes with the identifying calcification of the psammoma body, are observed beyond the ovary itself (Fig. 7). In such instances one is left with the choice between the assumption of very early implantation from an ovarian primary or of the multicentric origin of these structures from similarly predisposed areas of peritoneum.

(2) *Origin of Malignancy*

The question of the histogenesis of malignancy in the ovary is a somewhat different problem. Does cancer arise directly from the normal ovarian serosa or is there an intermediate stage of benign neoplasia, or a series of stages by which malignancy is eventually attained?

That a malignant papilloma may arise in a single loculus of an otherwise benign cystadenoma seems almost certain from the gross structure of some tumours and yet it appears at times that the serosal layer of the ovary is being transformed directly into highly complicated benign papillomas (Fig. 8) and, indeed, into fully malignant forms (Fig. 9).

The earliest stages in these transformations are almost invariably lost to observation by the overgrowth of the developed tumour, for there is no such opportunity afforded here to study pre-invasive lesions as there is for the cervix and endometrium.

(3) *Possibility of Change in Established Tumours*

The later stages in the evolution of ovarian adenocarcinoma can be studied with a greater chance of success. Here one is interested in the relative constancy of structure of a given tumour. Is an individual tumour, once fully established, to be regarded as analogous perhaps to a specific strain of micro-organism, constant in its biochemical functions and biological capacities or is there an increase in degree of malignancy? Do the cells of the metastasis or the recurrence behave as did the primary? Does the apparent acceleration in the downhill course of the patient depend upon an increase in the intrinsic malignancy of the tumour? The discussion of this problem will be delayed and considered later in relation to another characteristic of ovarian tumours, namely that of its varying degrees of differentiation.

(*B*) The Ascites Phase of Ovarian Carcinoma

Ascites, though occurring in the late stages of many neoplasms, is most characteristic of ovarian carcinoma. The detection of tumour cells in ascites fluid has become a diagnostic aid to the clinician and it has been assumed that the ascites fluid serves as a vehicle for the transport of cells from the primary lesions to points of implantation. Less thought has been given to the possibility of the ascites fluid as a culture medium for cell proliferation (Fig. 10).

More attention must now be directed to this phenomenon in ovarian carcinoma, because of the proven value in cancer research of the so-called "ascites tumours" as they have been developed in laboratory animals. Such tumours have afforded possibilities of a "quantitative oncology", since the cells, growing singly or in small clumps, are susceptible to counting.

The laboratory produced "ascites tumours" are somewhat different from those observed in human ovarian carcinoma but offer many points of similarity. The mouse ascites tumours are neoplasms entirely limited to the fluid medium, although they may have been derived originally from tumours that were characteristically solid. The concentration of cells per unit of fluid volume appears to be far higher in the laboratory ascites tumours than in the clinically observed forms.

One interesting question, that of why some carcinomas of the ovary proliferate in the ascites fluid and so perhaps why they metastasize through the peritoneal cavity, and others do not, receives a theoretical answer, from the work on animal ascites tumours. It has been shown that some transplantable laboratory tumours are readily converted by repeated inoculations into the ascites form, others with difficulty, while still others not at all (Klein and Klein, 1956). Once a tumour has been converted, however, continuous ready passage from animal to animal as an ascites tumour is possible. It is supposed that the process of conversion depends on the selection from the original population of cancer cells of a strain capable of proliferating in the relatively unfavourable environment of the ascites fluid with its low supply of oxygen and nutritive materials (Klein, 1955). Similarly it may be supposed that the ability of human carcinoma of the ovary to develop an "ascites phase" of growth with the associated tendency to widespread superficial implantation must depend upon some still to be discovered metabolic capacity of its cells.

In our own work we have collected material from the peritoneal fluid of 65 cases of carcinoma of the ovary. It is clear from the preliminary examination of this series that proliferation of cells in the fluid phase does occur as indicated by the presence of mitotic figures (Fig. 10). It is also evident that cells in the ascites fluid may appear singly or develop into small colonies of loosely aggregated cells (Fig. 11). We have not yet attempted a correlation between structure of the primary and the nature of the aggregations in the ascites fluid, although Koller (1956) reported that the colony-forming types seem to come from the more differentiated primary tumours. That in these cells one is observing cancer in the process of metastasis is a thought fascinating to the investigator and disturbing to the clinician.

(*C*) Implantation and Regression

The belief that malignant tumours may sometimes regress spontaneously has persisted in spite of the usually dubious authenticity of the reported cases. Faith in the possibility of "spontaneous regression" has been especially focussed on the papillary serous tumours of the ovary. Implants from these tissues certainly do at times disappear after surgical removal of the primary tumour. The question remains whether the cases in which this occurs are really cancer.

After the observation of this phenomenon in 5 cases on the Gynecological Service at Roosevelt Hospital (New York City) a review of the literature was undertaken and no less than 36 clearly proven or probable examples of such spontaneous regression were found (Taylor and Alsop, 1932). No doubt there have been a number of similar instances reported since that time for the occurrence appears not to be very unusual.

Study of the histology of the cases immediately available to us, and review of the reports and photomicrographs in the literature failed, however, to reveal a single instance of regressing tumours which could be described as "anaplastic" or even "fully developed" carcinoma in the histological sense. An example of a typical "implant" is shown in Figure 12, taken from a patient who in spite of widespread "seeding" of the peritoneum was known to be quite well some six years after an incomplete operation. The tumour was a highly organized, differentiated structure. Is this a benign, metastasizing adenoma or a malignant, regressing carcinoma?

What we are observing here is a tumour, biologically and histologically intermediate between the benign and malignant tumours. It has the capacity to proliferate rapidly, to be transmitted and perhaps to grow in ascitic fluid, and to fasten itself and briefly to grow on distant sites on the peritoneal surface. It seems, however, incapable of infiltration and indeed its life at the new site may be self-limited, for when the primary tumour as a source of new implants is removed, the implants disappear.

It appears then that, with the serous tumours of the ovary, an unbroken series of forms exists, beginning with the simple papillomas and progressing through these doubtful forms to the malignant cystadenocarcinomas, themselves of different degrees of de-differentiation and grades of malignancy. The line dividing the benign from the malignant is not a sharp one, but a gradual transition. Malignancy is not an entity, but a quality, possessed by tumours in varying degree. The varying malignancy within a series of tumours with a common histogenesis seems peculiarly susceptible to study in carcinoma of the ovary where histological evidence of degrees of differentiation is especially clear.

(*D*) The Phenomenon of Differentiation and Grade of Malignancy

The concept of different degrees of malignancy is at least as old as Virchow's work in 1858 and has lured a long series of clinical investigators (Harris, 1951; Graham, 1953). The gynaecologist is particularly familiar with the efforts to grade cancers of the cervix (Schottländer and Kermauner, 1912) and in general has gained the impression that the efforts have been unsuccessful or, at least, have led to no practical results. In spite of this, it is generally accepted that there are inherent qualities in each tumour which are largely

responsible for the tendency to invade and to metastasize and for the variable clinical course of the disease.

Among gynaecological neoplasms it also seems clear that, with respect to the adenocarcinomas of the endometrium and ovary, tumour structure has some bearing on prognosis. Many studies have shown that the highly differentiated adenocarcinoma of the endometrium, even termed by Ewing in 1940 "adenoma malignum", and certain tumours of the ovary of a borderline histological pattern have a prognosis far better than the average carcinoma of either type (Taylor, 1929; Taylor and Becker, 1947; Munnell and Taylor, 1949; Corscaden and Tovell, 1954; Munnell, Jacox and Taylor, 1957). The recognition of this difference is the beginning of the acceptance of the value of histological grading.

There are two excellent reasons why the grading of specimens of adenocarcinoma of the ovary should be more successful than the grading of epidermoid cancer of the cervix. (*a*) First, carcinoma of the ovary is characteristically a papillary structure, growing freely into a cystic cavity, filled with fluid, which, serving as a kind of culture medium, permits the tumour to assume the structure "natural" to it. Cancers of the cervix and indeed of most other sites are usually observed as clusters of invading cells, whose natural structural arrangement is modified by the tissues of the host with which it is in contact. (*b*) Secondly, the adenocarcinomas of the ovary are made up of a single type of cell whose variations depend on the malignant process alone, whereas the changes of malignancy in epidermoid cancer are complicated by the physiological efforts of the cell to evolve from the type found in the basal layer to that of the keratinized surface.

The grading of even these favourable tumours on the basis of tissue structure is still a far from precise process, but there can certainly be recognized (1) the benign papillary cystadenomas, (2) a group of borderline histology and uncertain clinical potential, and (3) several grades of malignant tumour. The distinguishing characteristics of these different grades have been frequently described (Taylor and Long, 1955). Examples of the several types of this ovarian tumour are shown in Figures 13 to 16, and a brief description follows.

(1) *Benign Papillary Serous Cystadenomas.* In the gross these tend to appear as low, warty, intracystic excrescences and, under the microscope, as broad based papillomas, often with much connective tissue, covered by a thin layer of inconspicuous columnar or cuboidal cells.

(2) *Borderline Papillary Serous Cystic Tumours.* The most acceptable examples of these are found in those cases already described in which peritoneal implants noted at the time of operation have regressed after removal of the primary tumours. Such tumours may be said to have demonstrated their "borderline" character biologically. Here the papillae under the microscope are apt to be of finer structure, more branching, but with a higher though still regularly arranged columnar epithelium.

(3) *Papillary Serous Cystadenocarcinoma.* Grade I. The papillary structure is still maintained, but in places the epithelium is apparently multi-layered. The cells are a little larger and rounder.

(4) *Papillary Serous Cystadenocarcinoma.* Grade II. The papillae mainly consist of multilayered masses of epithelial cells with only a thin core of connective tissue. The cells are round or polyhedral but in places there is still evidence of some polarity.

(5) *Papillary Serous Cystadenocarcinoma.* Grade III. The tumour now has the appearance of being a "solid" carcinoma, composed of sheets of cells. The cells have lost all relationship to a basement membrane. In practice it has been somewhat difficult to separate the last two groups, but there is little chance of confusing a grade III with a grade I.

The Problem of Consistency

One of the difficulties which beset the investigator who attempts the grading of tumours is the problem of consistency. First, there is the simple question of whether the tumour is the same in all its parts, and second, the more complicated issue of whether the tumour is consistent in its structure throughout its life history.

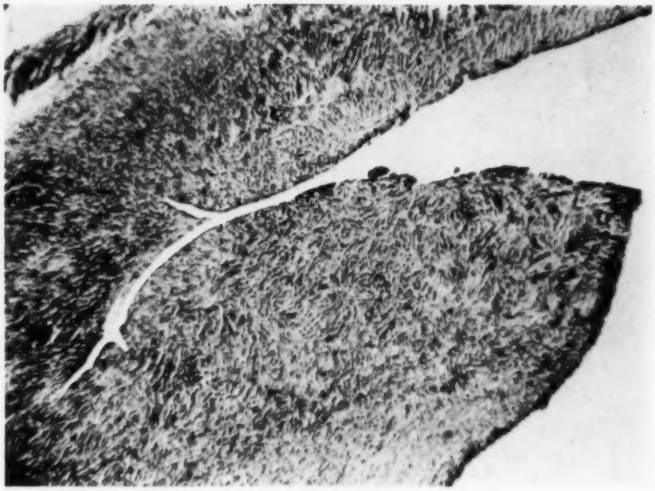


FIG. 4

Peritoneal invagination or serosa covered cleft in normal ovary. H. & E. ×50.

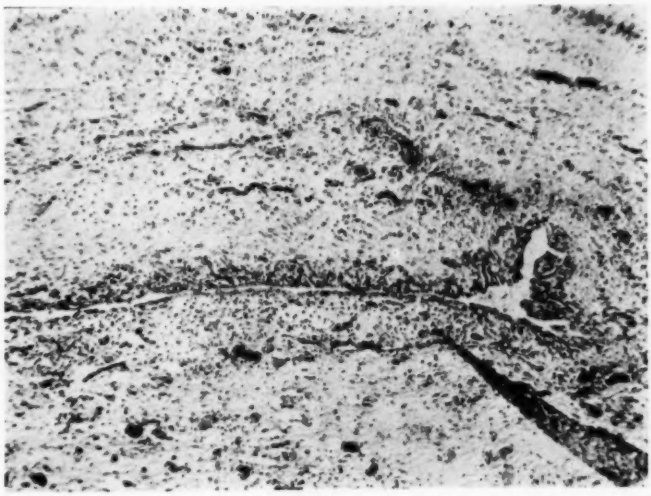


FIG. 5

Deep peritoneal invagination with larger cells and more complex branching. H. & E. ×60.

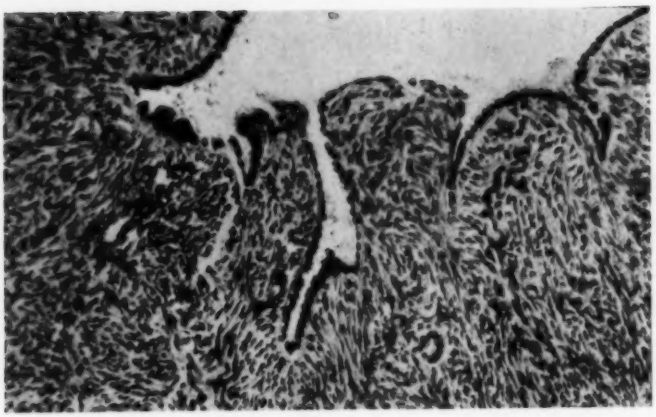


FIG. 6

Origin of simple papillary adenofibromas from peritoneal surface of ovarian cortex. H. & E. ×170.

FIG. 7

Peritoneal invaginations of tubal serosa. H. & E. ×396.

FIG. 8

Papillomatous transformation of ovarian serosa. H. & E. ×170.

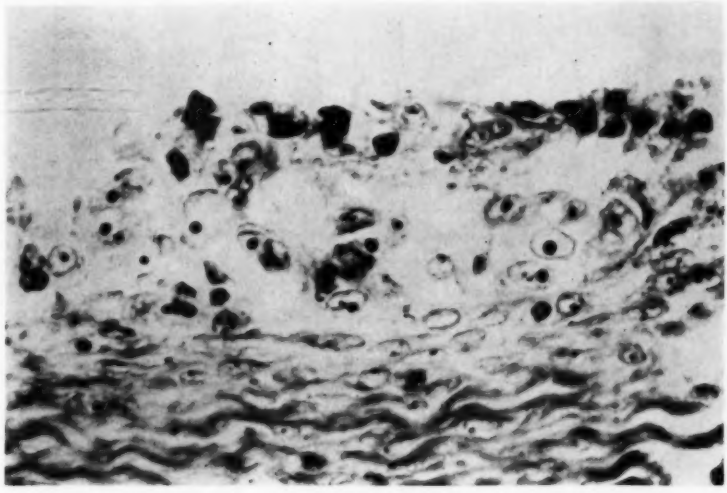


FIG. 9

Malignant transformation of ovarian serosa or surface extension of malignant cells. Masson. ×684.

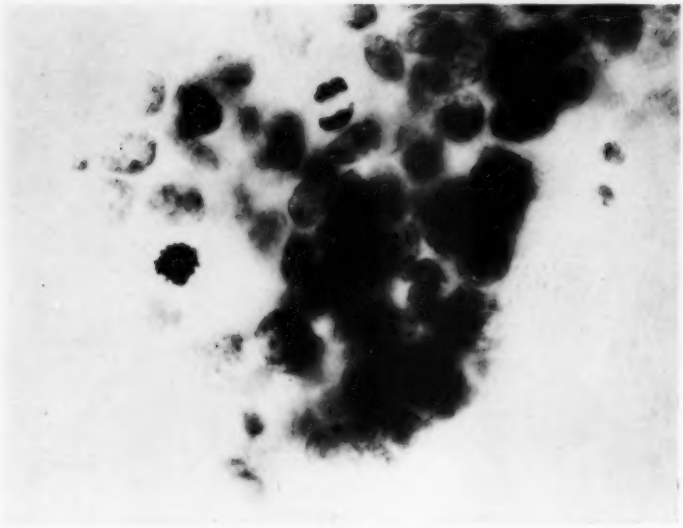


FIG. 10

A clump of carcinoma cells in ascitic fluid showing cells in metaphase and anaphase stages of mitosis. Feulgen. ×918.

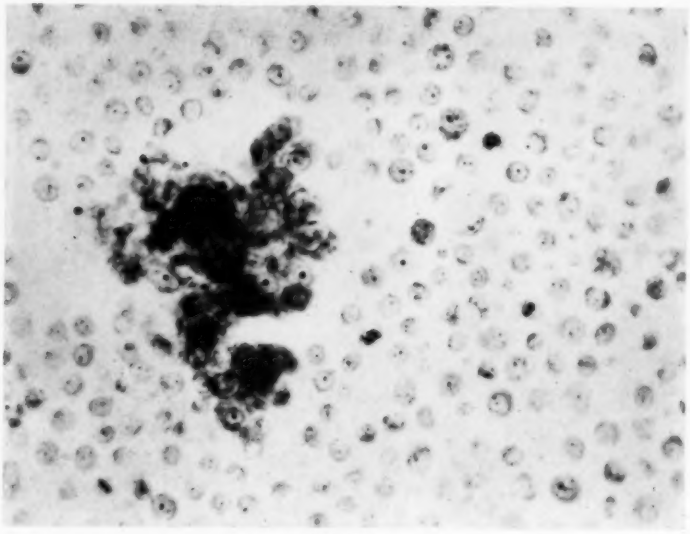


FIG. 11

Single cells and clumps of malignant cells, some in mitosis, in ascitic fluid. Methyl Green & Pyronin Y. ×324.

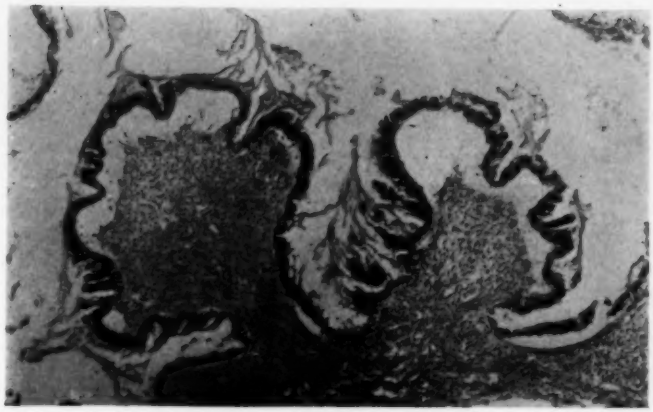


FIG. 12

Peritoneal implant in patient with six-year cure. (Reprinted from Taylor and Alsop.) H. & E. ×100.

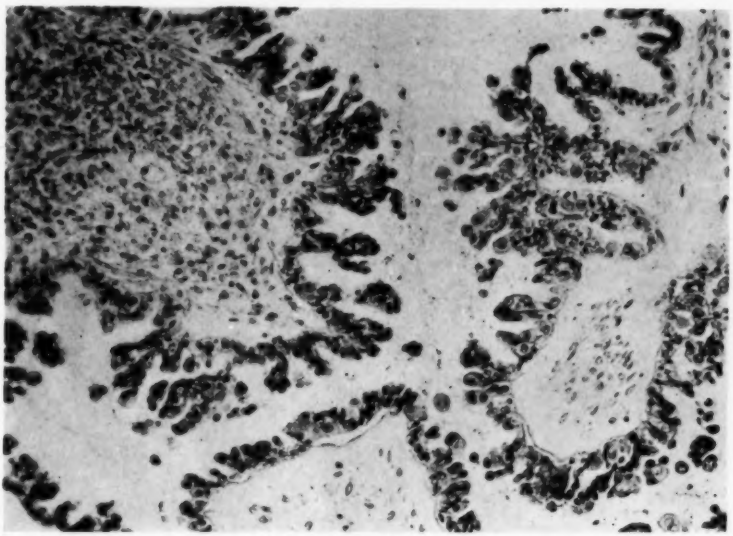


FIG. 13

Papillary serous cystadenocarcinoma, borderline. H. & E. ×170.

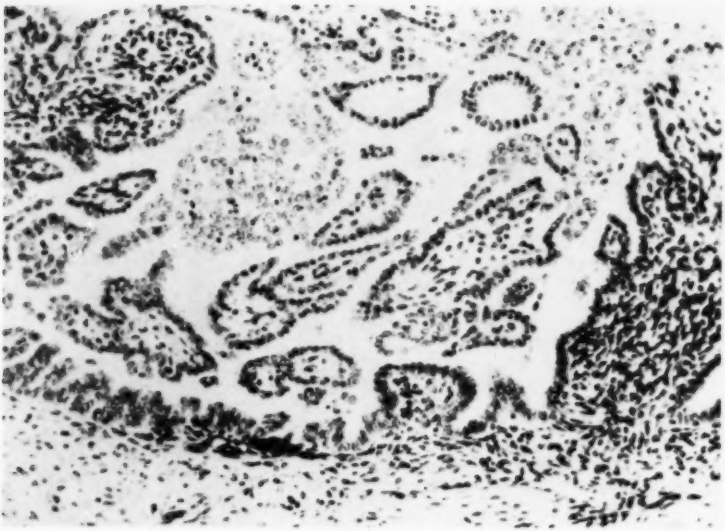


FIG. 14

Papillary serous cystadenocarcinoma, Grade I. H. & E. ×170.

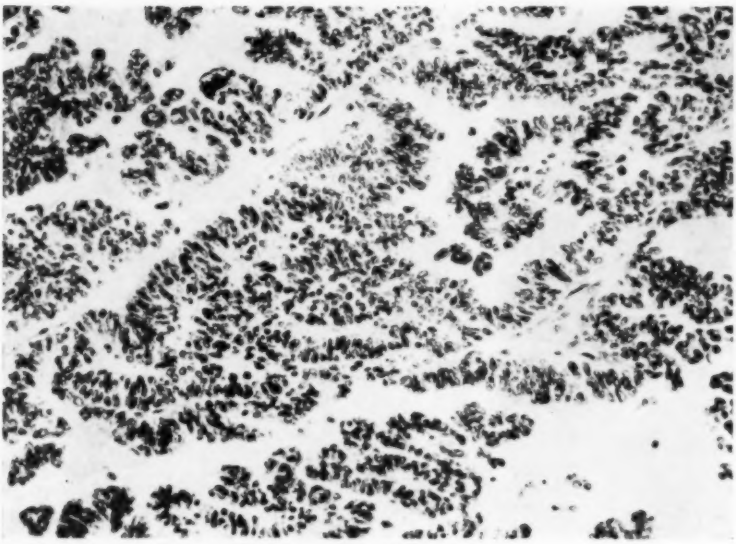


FIG. 15

Papillary serous cystadenocarcinoma, Grade II. H. & E. ×170.

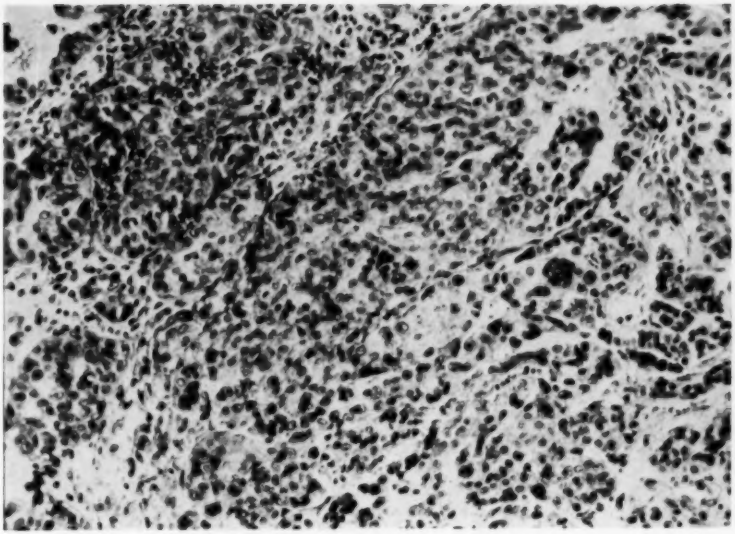
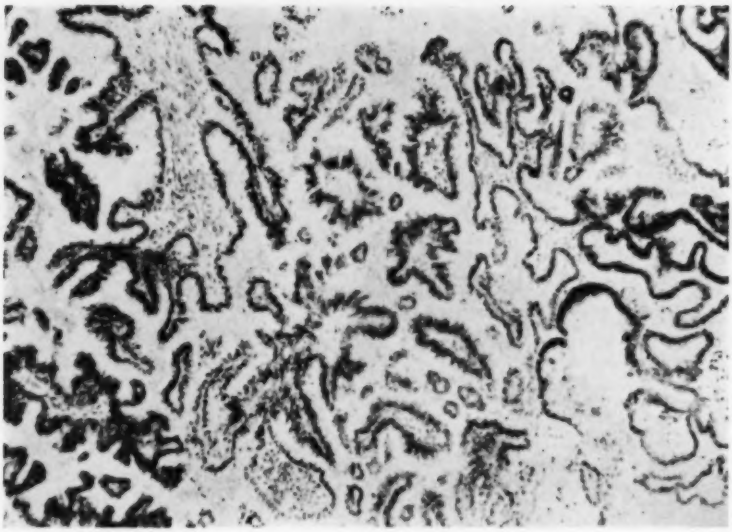


FIG. 16

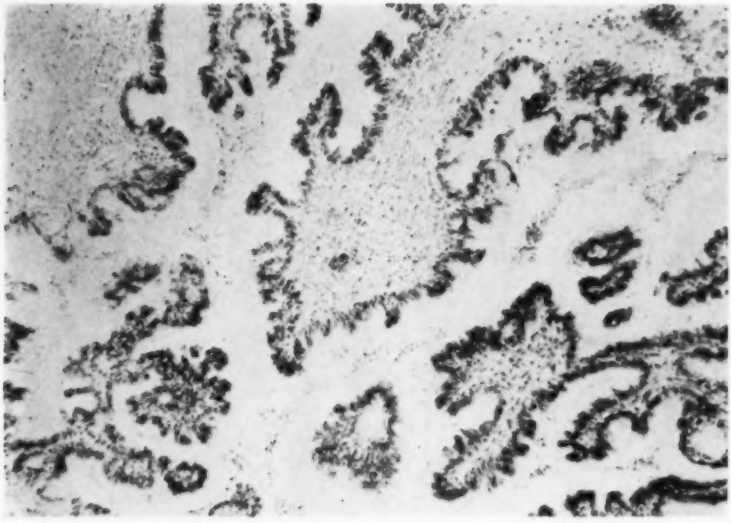
Papillary serous cystadenocarcinoma, Grade III. H. & E. ×170.

FIG. 17

Area of orderly appearing epithelium with cells of high grade of malignancy. H. & E. ×918.



(*a*)

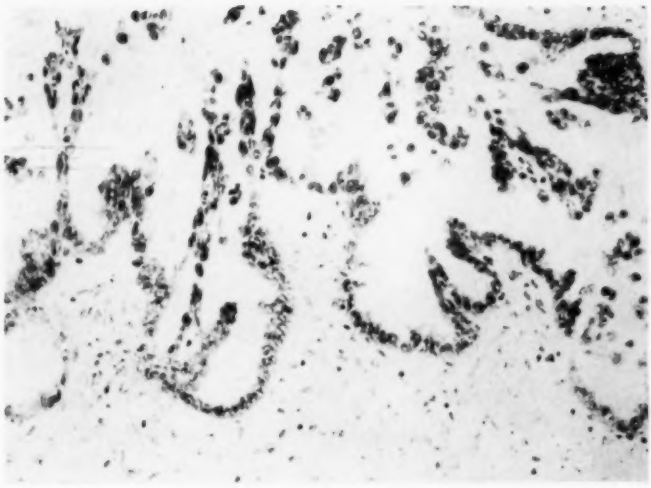


(*b*)

FIG. 18

Similarity of structure of (*a*) primary borderline tumour and (*b*) the mesenteric recurrence after an interval of six years. H. & E. ×112.

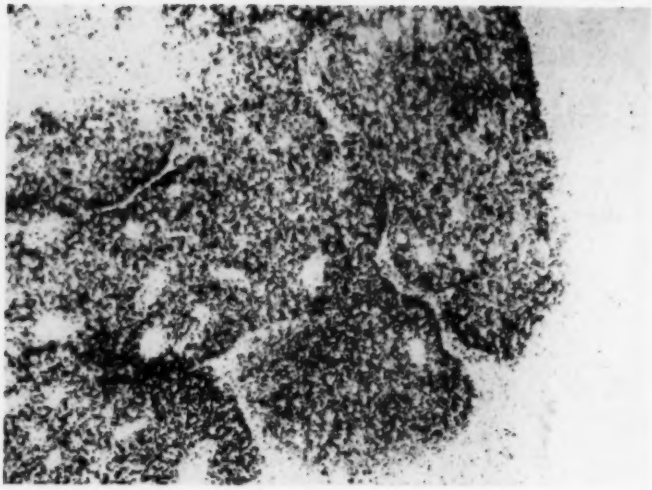
(*a*)



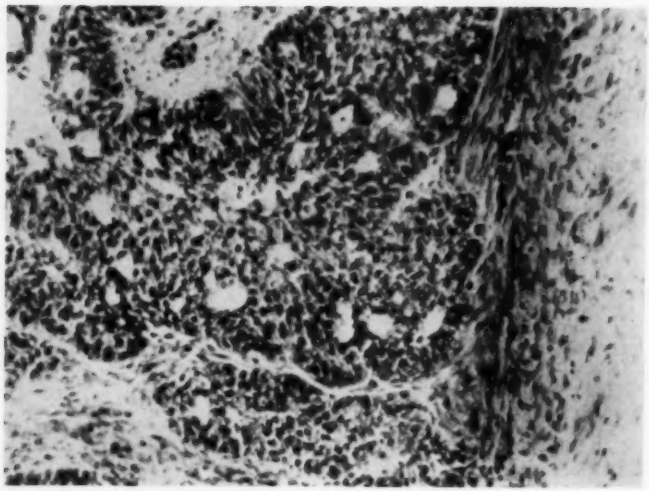
(*b*)

FIG. 21

Borderline type of papillary serous cystadenocarcinoma (*a*) reacted for succinic dehydrogenase and (*b*) an H. & E. preparation for contrast. ×162.



(*a*)



(*b*)

FIG. 22

Grade III papillary serous cystadenocarcinoma (*a*) reacted for succinic dehydrogenase and (*b*) an H. & E. preparation for contrast. ×162.

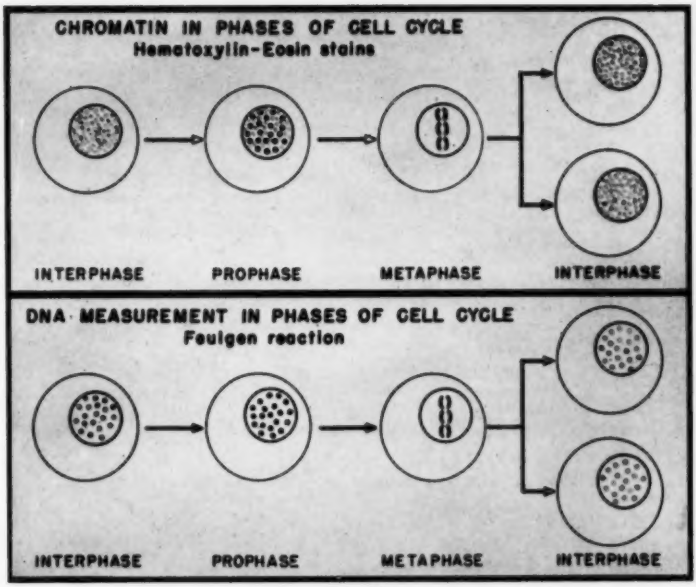


FIG. 24

Diagram of chromatin in phases of the normal cell cycle following H. & E. and the Feulgen reaction.

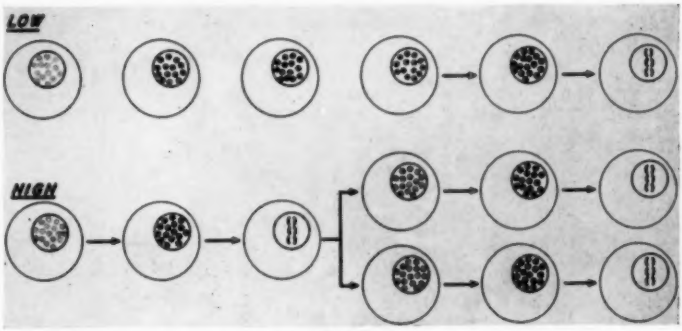


FIG. 25

Diagram of low and high mitotic index, an explanation of high DNA values.

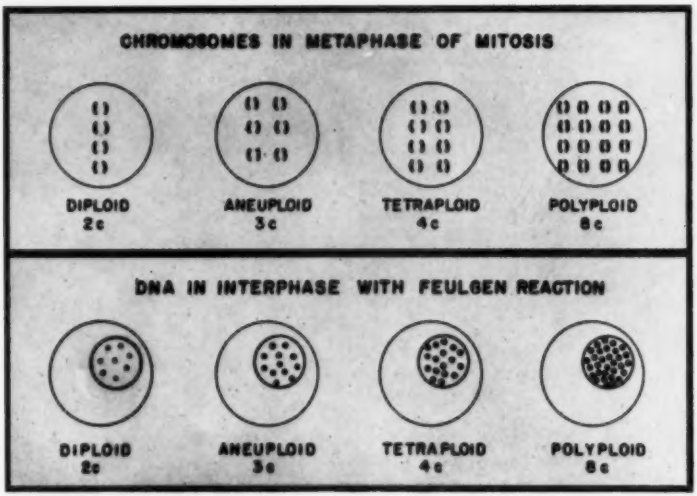
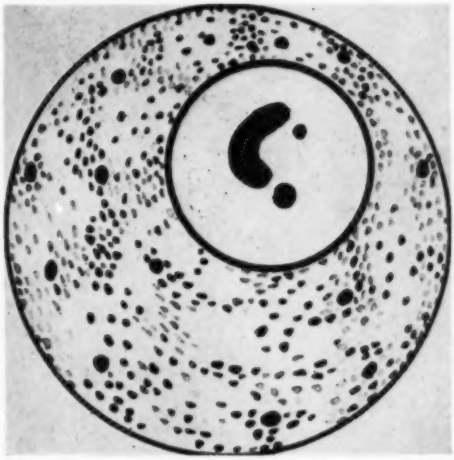


FIG. 26

Diagram of polyploidy in cells, an explanation of high DNA values.



RNA
Ribonucleic Acid

Methyl Green—Pyronin Y
Reaction

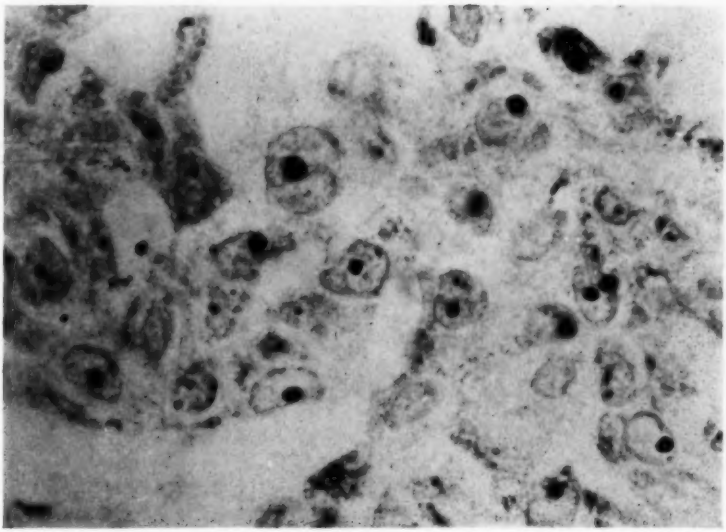
Nucleolus; cytoplasm
(chromosomes)

PROTEIN SYNTHESIS

FIG. 28

Diagram of RNA localization in the nucleolus and cytoplasm by the Methyl Green & Pyronin Y reaction.

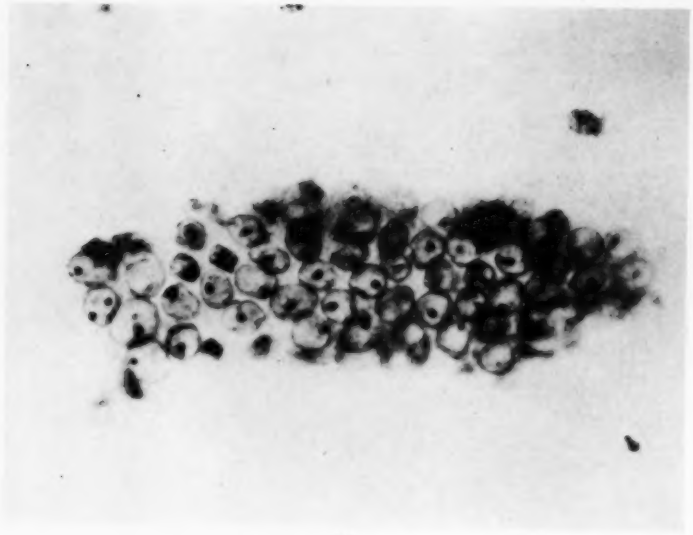
(*a*)



(*b*)

FIG. 29

Sections of papillary serous ovarian tumours for comparison of nucleolar size in (*a*) cystadenoma and (*b*) Grade III, Methyl Green & Pyronin Y. ×918.



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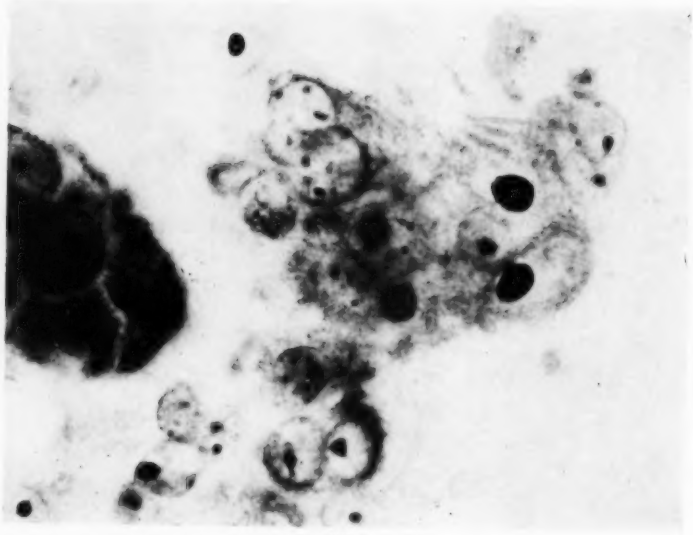

(*b*)

FIG. 30

Tissue smears of papillary serous ovarian tumours for comparison of nucleolar size and number in (*a*) Borderline Type and (*b*) Grade III, Methyl Green & Pyronin Y. ×918.

(a) *Consistency with Respect to Area*

Many observers, believing that they have detected differences in grade in even closely adjacent areas of the same tumour, have come to the logical conclusion that the grading of the tumour as a whole was not feasible. Our own work (Taylor and Long, 1955; Long and Taylor, 1956) has led to contrary conclusions, namely that the grade of the tumour is remarkably constant throughout its extent, and that a grade given to the tumour as a whole is, therefore, meaningful.

To arrive at such a conclusion requires the realization that the form which cellular interrelationship will take depends not solely on the intrinsic qualities of the cells but on the external environment to which the cells must adapt themselves. An identical tumour spreading over the inner surface of a cyst wall may express itself as a well-polarized epithelium and give superficially a well-differentiated appearance (Fig. 17), whereas this opportunity will be denied it in an omental or lymph node metastasis where it will grow in solid masses of cells.

With this principle in mind it was our opinion, after examining a total of 550 sections from different areas of 36 tumours, that a high degree of consistency existed (Table III). This conclusion required an evaluation of cellular morphology as well as of tissue structure and it is indeed our opinion that ultimate systems of grading will be based on cellular rather than tissue characteristics.

TABLE III

Ovarian Papillary Serous Tumours

Consistency of Grade in Different Areas of the Same Tumour

(Taylor and Long)

Histologic Grade	No. of Cases	Total Areas	Total Sections	Sections Consistent
Benign ..	6	23	66	66
Borderline ..	2	16	32	29
Grade I ..	6	35	122	122
Grade II ..	9	59	125	121
Grade III ..	13	82	205	188

(b) *Consistency with Regard to Time*

It is important also to know whether, in the long life history of the tumour, one is dealing with a constant organism with consistent characteristics, or whether degrees of malignancy change with the progress of the disease.

In the files of our hospital are 12 cases in which tissue was obtained both at a primary operation and at a subsequent one, the two procedures being separated from each other by 1 to 13 years (Fig. 18). In most instances the tumour structure remained identical even with long lapses of time and in no instance was there any certainty of change.

It appears then that in the papillary serous adenomas and carcinomas of the ovary one is dealing with individual entities which manifest a high degree of consistency, both with respect to the different areas of their extension and to the passage of time. This consistency permits one to begin the classification of individual tumours both for the practical purpose of prognosis and for the study of some factors underlying the quality of malignancy.

Clinical Results According to Grades

The practical importance of "grading" and the reality of the difference in clinical behaviour of the various grades is demonstrated in Figure 19, which shows the survival curves for 209

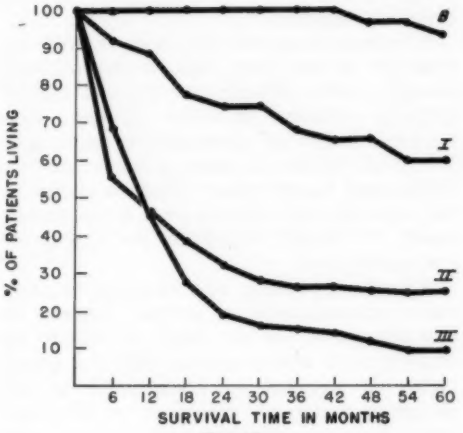

FIG. 19

Five-year survival curves. Papillary serous cystadenocarcinoma of ovary according to histological grade of malignancy at the Sloane Hospital, 1922–1953.

cases of papillary serous adenocarcinoma treated at the Sloane Hospital from 1922–1953. It will be noted that a group B, into which we have placed the cases of "borderline" histology has shown extraordinarily good results, but after four years, 2 recurrences with death have occurred. The grade III and grade II adenocarcinomas show similar unfavourable curves with three-quarters of all of the patients dead before the end of 2 years. The grade I cases fall between the highly malignant cases and those considered borderline.

The Significance of Degree of Differentiation

The existence of these identifiable types representing different grades of malignancy seems to offer a special opportunity not previously exploited in cancer research. Studies have indeed been made of the biochemical changes in tissue that occur at various stages in the course of experimental carcinogenesis. In a series of ovarian tumours one has a somewhat similar situation, but here for each individual tumour the process of neoplastic change has progressed to a given point of de-differentiation and there been arrested, the behaviour and potential of its cells remaining more or less constant thereafter.

It is apparent as one progresses through the spectrum of this series that, as morphologic changes occur, biologic function and clinical potential undergo correlated changes. Less obvious biochemical characteristics must alter in a parallel fashion. It seems probable then that biochemical factors which could be shown to vary quantitatively with the grade of the tumour would be closely related to the quality of malignancy itself.

With this hypothesis, we have set out to study various characteristics of ovarian tumours of different grades in the hope of identifying characteristics which, varying with the grade, might be regarded as fundamental to the malignant process. In this work we have met many technical difficulties which those more experienced might have avoided and turned up a few points, which indeed, we might have quite confidently predicted would be uncovered.

General Method of Approach to the Problem

The selection of techniques to be applied was up to a point opportunistic, since procedures have been utilized which have led to some success in the study of other neoplasms, especially animal tumours. The range of suitable methods was found to be somewhat limited, however, by special difficulties inherent in work with clinical material, which is often unpredictable in the time and quantity of its availability.

The programme has depended much upon histochemical and cytochemical methods, for these avoid some of the complexities which affect the biochemical studies of masses of tissue in which the specific malignant cells are mixed in varying proportion with connective tissue, vessels and other indifferent material. Nevertheless, an effort has been made to approach certain tissue functions with more than one technique.

The practical organization was rather simple. When a case suspected of having an ovarian carcinoma was scheduled for operation, the laboratory was notified and one of the investigators was present in the operating room to receive the specimen. This was taken at once to the tissue laboratory, where, after the pathologist received portions for diagnosis, suitable areas were separated and either frozen for future use or forwarded to the co-operating laboratories. Each of the laboratories then carried out its work independently, the results being correlated at a later date with the grade of the tumour determined on the basis of the histological criteria that have been listed.

Two large areas, in which something specific about tumour physiology seems already evident, concern tissue respiration and the nucleic acids of the cell. Some work has been done in both of these fields in the ovarian adenocarcinomas and will now be briefly reviewed. Details of the experimental procedures and results will be found in the reports of the individual investigators, most of which have been published.

Tissue Respiration and Glycolysis

The metabolic characteristic of tumour tissue which has been most consistently confirmed

since the culminating publications of Otto Warburg in 1930 is an abnormality in the oxidation of glucose. Warburg and his colleagues, by means of the manometric apparatus which he had devised, measured simultaneously the consumption of oxygen and the production of lactic acid. This was done in the presence of oxygen to measure so-called *aerobic glycolysis* and in the presence of nitrogen to measure *anaerobic glycolysis*. Both the studies of Warburg and many investigators repeating his work, have shown that tumours, as compared with normal tissues, display a high aerobic and anaerobic glycolysis (Weinhouse, 1955). Stated in another way, while normal tissues display predominantly an oxidative type of metabolism, tumours tend to ferment glucose with lactic acid as an end product.

The work on some thirty-seven papillary serous ovarian tumours in our Department has been carried out by Dr. Helena de Roetth (1957). Tumour tissue obtained from the operating room was prepared for immediate study in the Warburg apparatus, the average elapsed time of from 1 to 2½ hours having been shown to have no significant effect when the tissue was kept at 7° C. The tissues were sliced in 0·5 mm. sections and an average of 200 mg. was used for each Warburg vessel, each experiment having been run in triplicate.

Measurements were made of oxygen consumed and are expressed in Tables IV and V as QO_2, or μl. of oxygen and as QLa or μg. of lactic acid produced, each per mg. of dry weight of tissue per hour. Certain variables were introduced. In half the experiments, the gas phase in the vessel was air and in half, 100 per cent oxygen. In some experiments glucose was added to give a concentration of 100 mg. per cent.

TABLE IV

Oxygen Consumption and Lactic Acid Production in Serous Adenoma and Adenocarcinoma of Ovary

A. in Air (de Roetth)

Grade of Tumour	No. of Tumours	Oxygen Consumed QO_2		Lactic Acid Produced QLa	
			Added Glucose		Added Glucose
Benign	4	0·5	0·6	0·15	1·50
Borderline	2	2·3	2·1	0·00	3·80
Grade I	5	2·0	1·6	0·7	11·3
Grade II	11	2·3	1·9	1·1	13·0
Grade III	15	2·8	2·4	1·4	11·2

TABLE V

Oxygen Consumption and Lactic Acid Production in Serous Adenoma and Adenocarcinoma of Ovary

B. in Oxygen (de Roetth)

Grade of Tumour	No. of Tumours	Oxygen Consumed QO_2		Lactic Acid Produced QLa	
			Added Glucose		Added Glucose
Benign	4	·35	·45	0·15	1·0
Borderline	2	2·8	2·4	0·8	0·0
Grade I	5	3·0	2·0	0·0	18·8
Grade II	11	2·7	2·3	0·4	12·6
Grade III	15	4·0	3·4	1·0	12·0

Oxygen consumption was found to be lower for the benign tumours than for any of the malignant ones but there was little detectable difference between the grades of adeno-carcinoma (Table IV). Oxygen consumed was generally reduced with the addition of glucose, a phenomenon reported from other laboratories working with animal tumours (Olson, 1951; Brin and McKee, 1956). The lactic acid production in the absence of glucose was usually, but not consistently, greater for the malignant tumours, but with the addition of glucose the differences became striking. The lactic acid production with added glucose for each of the 31 malignant tumours was higher than for any one of the benign tumours.

When a gas phase of 100 per cent oxygen was used there was noted a general increase in oxygen consumption (Table V). The malignant tumours consumed more oxygen than the benign ones and again the QO_2 was somewhat reduced by the addition of glucose. The lactic acid production in the presence of 100 per cent oxygen was negligible but when glucose was added there was found to be a sharp difference between the benign and the malignant tumours.

In summary then, it is evident that lactic acid production, in the presence of added glucose, is a striking characteristic of malignant as compared with benign papillary serous tumours of the ovary. A clear correlation of this function with each grade of malignancy is, however, not apparent. If such fine differences really exist, these may be overshadowed in studies with human material by fortuitous differences in connective tissue content or in degrees of tumour degeneration.

Succinic Dehydrogenase and the Mitochondria

In some ways related to the processes of intracellular respiration are certain granules in the cytoplasm of the cell, known as mitochondria. These particles have been isolated and shown to contain an enzyme concerned with the oxidation of carbohydrates and in a general way with both the metabolic and proliferative functions of cells (Seligman and Rutenberg, 1951).

The demonstration of the intracellular sites of activity of the succinic dehydrogenase system is possible by means of a histochemical reaction based upon the reduction of certain tetrazolium compounds (Fig. 20). Application of this technique to material from 44 cases of ovarian papillary serous adenomas and adeno-carcinomas has been carried out in the Department at Columbia by Dr. Margaret Long, in a further attempt to find demonstrable cell functions that could be correlated with the degree of malignancy.

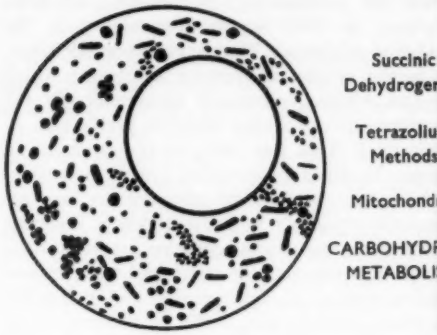

Fig. 20

Diagram of localization of succinic dehydrogenase in mitochondria by tetrazolium compounds.

The histochemical method for studying this enzyme requires immediate processing, the first steps being initiated within 10 minutes of the receipt of the specimen in the operating room. Unfixed frozen sections are cut from 5 mm. blocks of tissue, reinforced by gelatin to facilitate cutting. The sections are mounted on slides and immediately placed in the incubating solution.

In our laboratory we have utilized in the incubating solution two of the tetrazolium compounds as hydrogen receptors, neo-tetrazolium or NT (Rosa and Velardo, 1954), and, more recently, Nitro-BT (Nachlas *et al.*, 1957). These substances in the presence of excess succinic substrate are reduced by the enzyme system in the cells to a purple-black formazan compound in the cytoplasm at the site of activity. Nitro-BT is considered superior

to NT in that it results in evidence of the localization of the enzyme system in the mitochondria and in elimination of artifacts.

The results, to the extent that we had hoped for a key to the problem of grades of malignancy, have been disappointing. A borderline type of tumour is shown reacted for succinic dehydrogenase on the right side of Figure 21, a haematoxylin-eosin preparation being shown on the left for contrast. The sites of activity of the succinic dehydrogenase are clearly shown in the purple-black granules scattered through the cytoplasm of the epithelial border of the papillae. A similar preparation for a grade III cystadenocarcinoma is shown in Figure 22. Attempts to contrast the amount or the distribution of these granules have failed to reveal consistent points of distinction between the different grades of adenocarcinoma or even between the benign and the malignant tissues. A lack of this enzyme is certainly not responsible for the defect in glucose metabolism noted in tissue respiration studies. The reservation must be made, however, that the histochemical reaction for succinic dehydrogenase probably demonstrates a group of enzyme substances and the lack of a specific one might still be present to interfere with the final stages of glucose utilization.

The Nucleic Acids and Tumours

It is to the nucleus of the cell, however, that the investigator of the cancer problem eventually turns. Here one enters an area, mysterious, perhaps even a little mystical, and quickly meets the problem of the two nucleic acids.

Ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) are complex organic compounds, polynucleotides, composed of purines, pyrimidines, phosphoric acid and an identifying sugar, a ribose or desoxyribose. In the cell, nucleic acids occur in combination as nucleoproteins and, undoubtedly, in a great diversity of complicated forms. In a very general sense, distinct functions can be assigned to DNA and RNA and they may be distinguished in microscopic sections of tissues or smears of cells by appropriate staining reactions.

DNA is one of the basic components of the chromatin and is considered to be the carrier of the hereditary qualities of the cell. RNA, distributed most conspicuously in the nucleolus and cytoplasm, is thought to be concerned with protein synthesis.

Incorporation of Radiophosphorus (P^{32}) into Benign and Malignant Ovarian Tumours

Since phosphorus is an essential part of the nucleic acids and its radio-isotope P^{32} can be readily measured, the turnover or synthesis of DNA and RNA can be determined by measuring the rate of incorporation of P^{32} into tumour slices. The procedure has been carried out in a small group of cases in our Department by Dr. Dudipala Reddy and his associates (Reddy *et al.*, 1957).

The technique employed requires first, the immediate cooling of the specimen in crushed ice and later, incubating in a Warburg apparatus with 3 μc. of P^{32} per gram of tissue for 3 hours. Chemical procedures separated the RNA, DNA and lipid fractions and these were then counted for P^{32} activity.

The accompanying Table (Table VI), somewhat simplified from the original, gives the results. Three points may be noted. (1) As shown in the last column there is a large variation in the turnover values for phospholipides with no apparent relation to the malignancy of the tissues. (2) With DNA the differences in the rates of incorporation are of small magnitude, although with the single exception of the grade I case the values are higher for the malignant tumours. (3) The incorporation of the P^{32} into RNA is consistently higher in all of the malignant tumours than in the benign ones.

These findings are not surprising since previous studies by several investigators have demonstrated high rates of P^{32} incorporation into embryonic or neoplastic tissues and have shown that after the experimental use of carcinogenic agents the uptake of P^{32} by liver is greatly increased (Griffin *et al.*, 1951). The findings on this point, in this small series of cases, for both DNA and RNA synthesis receive interesting corroboration in the spectrophotometric and histochemical studies now to be reported.

TABLE VI

In Vitro *Turnover of Phosphorus Compounds in Ovarian Tumours*
(Reddy)

Type and Grade of Tumour	Relative Specific Activity		
	Ribonucleic Acid	Desoxy-ribonucleic Acid	Phospho-lipides
Granulosa cell tumour:			
Benign	4·27	0·73	15·35
Pseudomucinous cystadenoma:			
Benign	2·34	0·62	
Papillary serous cystadenocarcinoma:			
Grade I	9·25	0·41	25·60
Grade II	22·60	2·43	23·50
Grade II	29·20	1·08	10·10
Grade II+	10·70	2·12	8·02
Grade III−	15·00	1·12	11·40
Grade III	15·05	1·59	16·20
Animal controls:			
Normal rat liver	4·27	0·27	24·90
Adenocarcinoma 755	6·10	2·54	
Ehrlich ascites ca	28·20	4·82	

VARIATIONS IN DNA CONTENT OF THE CELLS

Observers of conventionally stained sections of cancer tissue have long been impressed with the frequency of mitotic figures, by the often atypical appearance of these structures and in general by what they have called the "hyper-chromatism" of cancer cells. Attention has been increasingly directed toward this phenomenon, since a cancer cell is often regarded as a "mutant" and the hereditary characteristics of the cell reside in the chromosomes. A number of techniques may be applied to the study of the chromosomes among which is the spectro-photometric measurement of the DNA.

In reporting the results of the studies carried out in our Department, by Dr. Saul Bader (1959), on the measurement of DNA in a series of tissues from carcinomas of the ovary, it is necessary to review certain terms and principles in a series of diagrams. This is to risk presenting very elementary material but, to judge from personal experience, in attempting to recall half-forgotten principles and to acquire an understanding of new ones, this step is nearly essential for most clinicians and part-time pathologists.

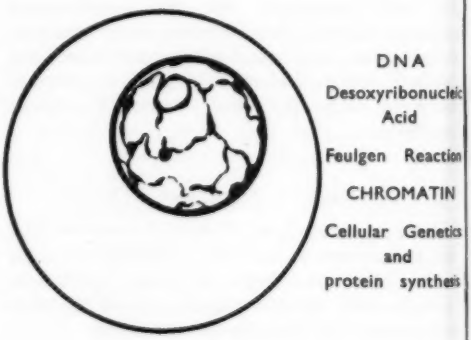

FIG. 23

Diagram of localization of DNA in chromatin as demonstrated by the Feulgen reaction.

The first diagram of this group (Fig. 23) illustrates simply the localization of the DNA in the chromatin of the nucleus and its demonstration by the Feulgen reaction. This cytochemical reaction is considered to be specific for DNA (Feulgen and Rossenbeck, 1924).

The second diagram (Fig. 24) follows the DNA as chromatin through the phases of the

cycles of cell division, in the upper series as demonstrated in a haematoxylin-eosin stained preparation and in the lower, by the more specific Feulgen reaction. It is to be noted that, in the interphase, the Feulgen staining is relatively pale. In the prophase, the reaction becomes more intense, as more chromatin material or DNA is synthesized in preparation for mitosis. Cell division then occurs and two new cells with the quantity of DNA characteristic of the interphase result. The varying amounts of chromatin in individual cells may be accurately determined by the spectrophotometer and the cells classified according to their DNA content.

The so-called hyperchromatism of cancer tissues can be accurately measured by this technique, but may actually have two causes.

(1) *The Mitotic Index*

The next diagram (Fig. 25) shows that the rapidity of cell division will affect the percentage of cells with high DNA values. In the upper series of the diagram, a cell is dividing slowly and there is only one cell in the prophase where increased DNA synthesis has provided an intense Feulgen reaction. If the rate of cell division is increased, as indicated in the lower series, there will be many more cells caught in the prophase and the percentage of cells with high DNA values correspondingly increased.

(2) *Polyploidy*

The fourth diagram in this series (Fig. 26) shows how an abnormal number of chromosomes, an anomaly frequently seen in tumour tissue, may also affect DNA content.

The number of chromosomes in each cell is characteristic for each species and since these structures occur in pairs the normal condition is known as "diploid". Under certain circumstances the chromosome number may increase without cell-division and there results various abnormalities, termed "polyploidy" when there are multiple sets of the diploid number and aneuploidy for irregular deviations from the normal. A common anomaly is tetraploidy, in which there are twice the normal diploid number.

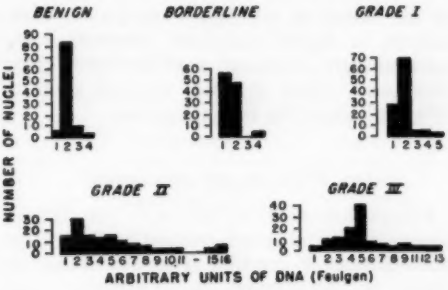

FIG. 27

Histograms of papillary adenomas and carcinomas of the ovary (Bader).

In some species, especially those lower than the mammals, ploidy can be determined by actual counting of chromosomes in tissues. In mammals, like man with his 46 chromosomes (Tjio and Levan, 1956), this is impossible without the use of special techniques. An alternative approach to the determination of ploidy in man is the analysis of amounts of DNA in the interphase nucleus by the spectrophotometer.

The results of a study of the DNA content of the cells in ovarian tumours are depicted in the histograms of which those in Figure 27 have been selected as fairly typical from the 24 cases that have been investigated. In these diagrams, there is shown the number of nuclei corresponding to each DNA class among the hundred cells studied spectrophotometrically in each case. Thus, in the example selected to show the benign group, 90 per cent are diploid cells, indicating little cell-division and probably no polyploidy. The two "borderline" and grade I cases varied somewhat but showed no clearly significant differences, with the nuclei containing chiefly the diploid amount of DNA. The grade II and grade III tumours show, however, marked variability in DNA range, compared with the other groups, but in particular tend to show some cells with very high values, up to as much as eight times the normal content.

It appears then that in the most undifferentiated ovarian papillary cystadenocarcinomas not only is mitosis frequent, as indicated by the large number of tetraploid values, but there is also a high incidence of polyploidy as indicated

by the values in the higher categories. These findings in highly malignant carcinomas are quite strongly contrasted with the lower grade carcinomas which in other respects seem to differ little from the benign tumours.

The RNA of the Nucleolus

Ribonucleic acid (RNA) may be demonstrated in the cell cytochemically by the methyl green-pyronin Y reaction (Fig. 28). It can be shown to be present in apparently small quantities about the chromosomes and in the cytoplasm and concentrated in larger amounts in the nucleolus. The nucleolar apparatus is believed to be the source of new protein in the cell-tissues and in some, especially in those of the renal adenocarcinoma of the frog (Duryee, 1956), there is evidence of the discharge of RNA nucleolar material into the cytoplasm.

The nucleolus has been recognized as a prominent feature of malignant cells for many years (Pianese, 1896) and comment has been made upon the presence of such large nucleoli in the cells of adenocarcinomas of the ovary (Taylor, 1929). The finer morphology of the nucleolus in cells of malignant tumours has been the subject of a recent study, based in part on the carcinoma of the ovary material of this series (Kopac and Mateyko, 1958). The observations of these investigators were made on living cells growing in tissue culture as well as on conventional fixed material. They describe striking variations in the structure of the nucleoli of malignant ovarian cells and nucleolar extrusion into the cytoplasm.

Work completed in our laboratory under the direction of Dr. Margaret Long appears, however, to have been the first to study this problem quantitatively and to show the nearly perfect correlation between nucleolar number and size and grade of malignancy. The differences in nucleolar dimensions and intensity of RNA staining between the adenomas and the different grades of the papillary serous tumours are at once strikingly apparent from comparison of methyl green and pyronin Y reacted tissue sections, equally magnified (Fig. 29). The contrast is similarly apparent in whole cells of tissue smears (Fig. 30).

The nucleoli may with patience be counted and averages computed for each case and ultimately for each grade of malignancy. In Table VII are shown the percentage of cells in each grade containing certain numbers of nucleoli. These figures are based on a count of the nucleoli in 200 cells of each of 36 cases of papillary serous adenoma and adenocarcinoma. The tendency to an increasing number of nucleoli with grade of malignancy is quite clear.

Table VII

Ovarian Papillary Serous Tumours
Multiple Nucleoli Per Nucleus Per cent
(Long and Taylor)

Histological Grade	No. of Cases	No. of Nucleoli Per Nucleus			
		2	3	4	5+
Benign ..	7	86·0	12·5	1·5	
Borderline	2	67·5	26·5	6·0	
Grade I ..	6	52·0	32·5	12·0	3·5
Grade II	10	41·0	27·0	19·0	13·0
Grade III	13	27·5	20·5	16·0	36·0

The average diameter of the nucleoli in each grade has also been determined, using an ocular micrometer, a method which for nucleolar RNA at least may be regarded as giving a measure of RNA content at least as accurate as could be obtained through the use of the spectrophotometer. The results again show a correlation between nucleolar RNA and grade of malignancy which, when statistically analyzed, is surely significant (Table VIII).

When the factors of number and of size of nucleoli are viewed together it seems evident that the malignant cell has far more RNA than the benign one and that, in a fairly definite sense, RNA content is related to histological grade of malignancy. These measures of RNA content represent the most striking correlation we have yet found between a biochemical characteristic and degree of malignancy. To the extent that our original hypothesis is correct, namely that any cell function found to vary consistently with degree of malignancy would be one of the factors concerned with the quality of malignancy itself, then the amount of ribonucleic acid per nucleus appears to be closely related to this quality of tumour tissue.

TABLE VIII

Ovarian Papillary Serous Tumour
Single Nucleoli Per Nucleus: Mean Diameter
(Long and Taylor)

Histological Grade	No. of Cases	Mean±SEm Microns	Grade Comparisons	Probability (Per cent)
Benign	7	1·3±·01	Benign vs. Borderline	<0·1
Borderline	2	1·5±·01	Borderline vs. I	62·0
Grade I	6	1·5±·01	I vs. II	1·0
Grade II	10	2·0±·02	II vs. III	<0·1
Grade III	13	3·0±·02	Benign vs. III	≪0·1

GENERAL COMMENT

The experience of the last seven years, in our work with the adenocarcinoma of the ovary, has taught us a number of things. Perhaps it would be better to say these have been re-emphasized for essentially everything we have reported has been chiefly the application to a special situation of what was already known.

(1) The carrying over from the laboratory of principles demonstrated in basic science work to the level of clinical medicine offers a major opportunity as well as responsibility. It is necessary as a check upon the validity and applicability of basically derived concepts and is essential to the continuing education of the clinician. It provides for the cross fertilization as essential for the proliferation of ideas as for that of organisms.

(2) The collaborative work of the basic science investigators with clinicians is at least one of the ways by which the work of laboratory and clinic may be brought into closer relationship. Such collaboration is not always easy and requires an unselfish recognition of the contributions which each group may make and an equitable division of the rewards. Much more could be written on this topic.

(3) The importance of adenocarcinoma of the ovary has been stressed. Not only has work upon this been less than its frequency deserved, but this tumour offers for the worker on cancer in general the opportunities of an observable histogenesis, of the existence of an "ascites phase" where proliferating cells may be observed in the natural culture media of the peritoneal fluid, of the phenomenon of spontaneous regression of a tumour that seems to be transitional between the benign and the malignant and, finally, an opportunity seemingly unequalled among human tumours of studying the essential phenomenon of neoplasia, that of differentiation.

(4) The importance of this process of differentiation and de-differentiation or of varying degrees of malignancy has been re-emphasized. The value of a concept of malignancy as a quality variably present, rather than as an entity, has been proposed again. The suggestion has been made that the test of a biological or biochemical process, characteristic of malignancy, would be its quantitatively variable presence in relation to degree of differentiation.

(5) Finally, report is made of early efforts to find such processes that could be so correlated. Differences between the benign and the malignant were found in respect to tissue respiration, rate of P^{32} incorporation in RNA and in the variability in amounts of DNA. Nucleolar size and number, probably a rough measure of ribonucleic acid content, seemed to bear a consistent relationship to the grade of malignancy.

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THE CONTRIBUTION OF RADIOTHERAPY TO THE MODERN TREATMENT OF FEMALE PELVIC CANCER

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No other field offers a greater use for radiotherapy than does the treatment of malignant disease of the female genital tract. With one exception all the major lesions present the opportunity for using radiotherapy as an alternative to surgery, or as a means of improving the result of treatment by combining the two methods. With regard to cancer of the cervix, thirty years ago, when we established a joint clinic between the Department of Obstetrics and Gynaecology and the Ontario Institute of Radiotherapy at the Toronto General Hospital, our previous experience prompted us to adopt radiotherapy as routine treatment as it held the prospect of a higher cure rate and freedom from the serious complications which were associated with surgical treatment at that time. This opinion, though modified under present conditions, governs the treatment of cervical cancer today.

In Canada, the major role in the provision of public health is under provincial control. On this basis the Ontario Cancer Treatment and Research Foundation maintains seven radiotherapy centres, four of which, including the Princess Margaret Hospital, Toronto, are associated with teaching hospitals of medical schools in Toronto, Ottawa, Kingston and London, and three others are associated with large general hospitals in Hamilton, Windsor and Port Arthur. These centres are situated so as to provide a province-wide service, and are organized so that the radiotherapists have the benefit of consultants from the medical and surgical specialties co-operating in the care of the patients. Uniform records are maintained in the clinics and these are reviewed annually by the Statistician to the Foundation and reported by him on a combined basis. Clinical Conferences of the staffs are held each year, and in October of this year Cancer of the Cervix is to be reviewed. I have been permitted to present two tables which show the result of treating this lesion in the combined clinics in the twenty years from 1933 to 1952.

Table I shows the improvement in the five-year survival rate. The increase from 32 to 45 per cent indicates that instead of 725 patients surviving five years in the period 1948 to 1952 only 515 would have survived on the basis of the rate which was obtained in the first five-year period.

TABLE I

Improvement in Survival Rates, 1933–1953

Period	Number	Five-Year Survivors		Per cent Untraced at Fifth Anniversary
		Number	Rate	
1933–37 ..	480	154	32·1	2·5
1938–42 ..	1,033	355	34·4	1·8
1943–47 ..	1,303	539	41·4	2·4
1948–52 ..	1,609	725	45·0	4·0
Total* ..	4,425	1,773	40·1	2·8

* Carcinoma Stage O (Carcinoma *in situ*) is excluded from all tables.

TABLE II
Improvement in Survival Rates by Clinical Stages, 1933–1953

Period	Stage I			Stage II			Stage III			Stage IV		
	No.	Five-Year Survivors		No.	Five-Year Survivors		No.	Five-Year Survivors		No.	Five-Year Survivors	
		No.	Rate		No.	Rate		No.	Rate		No.	Rate
1933–37	96	62	64·6	197	70	35·5	152	21	13·8	29	—	—
1938–42	177	117	66·1	413	167	40·4	341	66	19·4	90	3	3·3
1943–47	338	220	65·1	509	229	45·0	370	81	21·9	64	2	3·1
1948–52	473	324	68·5	639	293	45·8	362	94	26·0	120	7	5·8
Total	1,084	723	66·7	1,758	759	43·2	1,225	262	21·4	303	12	4·0

Table II shows that whereas there has been a modest increase in salvage of patients with Stage I lesions the improvement in the treatment of Stage II and particularly Stage III lesions is highly significant. The favourable progress may be attributed to more effective external irradiation to the tumour which has extended beyond the primary site. Improvements in radiotherapy techniques have to some extent kept pace with those of surgery. The advent of the radiation physicist has resulted in greater precision in beam direction and depth dose mensuration. This provides a basis for individualization. Just as the empiric methods of twenty-five years ago were succeeded by routine estimation of depth dose conforming to an accepted standard, so now the study of the patient with regard to variations consequent on the growth of the tumour and anatomical peculiarities eliminates inaccuracies which often result from applying laws of average.

The effect of these measures on the cure rate may be assumed, but the effect on the incidence of radiation injuries is readily demonstrated. Two figures are shown of three-dimensional models used in some of the clinics. By this means the positions of the radium applicators are clearly indicated, and any deviation from the normal position of the cervix is noted, so that an accurate estimation of the dose at points "A" and "B" is determined, and the heavily irradiated area can be effectively protected by a movable lead strip during the subsequent external radiation. The danger of over-irradiation of the rectum and bladder is decreased by the use of a probe dosimeter. Figure 2 which includes the position of the ureters shows their variable relationship to the cervix. This indicates the great difficulty which is often experienced in not including the ureters in a heavily-radiated area.

Table III shows the incidence of post-radiation complications occurring in patients treated in one of the clinics before and after the adoption of this technique. The injuries affected the urinary and intestinal tracts, and in 4 patients degenerative changes occurred in bone resulting in pathological fracture of the neck of the femur in 3 cases. It is interesting to note that in the same clinic over the same periods of time major post-operative complications have practically doubled with a more radical surgical programme.

TABLE III
Post-Radiation Injuries

Period	Patients Treated	Patients Injured	Per cent Incidence
1940–54 ..	271	15	5·5
1955–57 ..	68	1	1·5

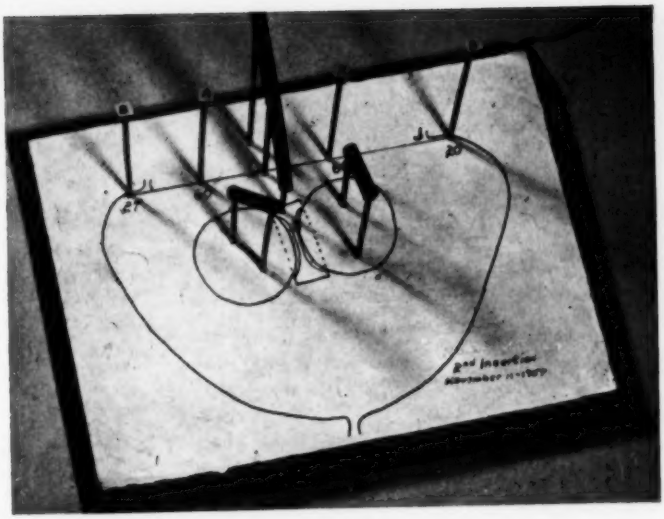

FIG. 1

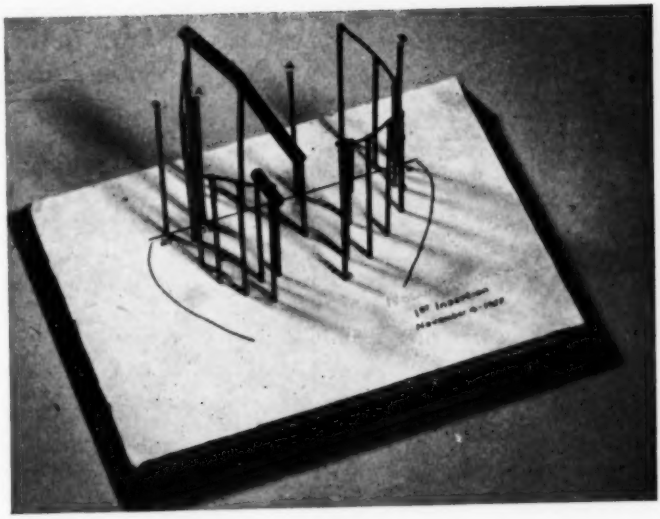

FIG. 2

A second factor contributing to better therapy is the use of super-voltage equipment. In Ontario all the clinics are provided with Cobalt^{60} kilocurie units, and in addition, a 24 Mev. Betatron is in use at the Princess Margaret Hospital. However, all this equipment has been in use for too short a period to allow a detailed appraisal of its effect. All are agreed that it has fundamental advantages over conventional X-ray, such as skin-sparing effect, less absorption by the bony pelvis, a more constant source of energy and that it provides a more homogeneous irradiation of a mass of tissue. Reports have been published elsewhere (Rutledge and Fletcher, 1958; Blomfield, 1959; Watson and Binkell, 1959) indicating considerable advantage in very heavy patients, and in the treatment of more advanced lesions approaching the stage of a frozen pelvis. While awaiting evidence which time alone can provide, as a gynaecologist one inclines to the opinion that the careful application of standard therapy, with consideration of all the variations that a tumour may present in every individual patient, is of greater importance than the possibilities which ever-increasing voltage may contribute to the ultimate cure rate.

There is another factor of great importance contributing to the improvement in the survival rate, namely a better distribution of case material. In order to present two groups of patients with generally favourable or unfavourable tumours, Stage II lesions were divided into Stage IIA, consisting of slight involvement beyond the cervix into the parametrial and paravaginal tissues or on to the vault of vagina, and Stage IIB, consisting of those cases in which there was considerable extension, but falling short of the side wall of pelvis or the lower third of vagina. An "early" group, consisting of Stage I and IIA is compared with an "advanced" group, including Stages IIB, III and IV.

Tables IV and V compare these two groups. The study was made at the Clinic at the Toronto General Hospital* on 1,708 patients treated in the last 23 years, 554 of the patients being treated in the last five years.

From this study it is clearly demonstrated that the improvement in case material is a major factor in the improved salvage rate. It would be inopportune to consider the possible factors which have been responsible for more patients coming for treatment with "early" lesions. The question may well be dismissed as a product of a more enlightened public and a more alert profession.

The Failure to Cure "Early" Carcinoma

One is always concerned with failure to cure patients with so-called "early" lesions. However, it should be remembered that if one follows the rule that doubtful cases must be included in the earlier stage, Stage I lesions are

TABLE IV

Survival Experience: 1930–47 vs. 1948–52

Stage	Per cent by Stage		Net Survival Rates	
	1930–47	1948–52	1930–47	1948–52
I, IIA ..	41·4	56·4	59·3	61·3
IIB, III, IV	58·6	43·6	20·7	24·4
Total ..	100·0	100·0	36·7	45·0

* This Clinic has now moved to the Princess Margaret Hospital.

TABLE V

Improvement in Survival Rates: 1930–47 vs. 1948–52

(Percentage in brackets)

Observed survival rate 1930–47	36·7		
Observed survival rate 1948–52	45·0		
Difference		+8·3	
Expected survival rate at 1930–47 Stage rates	42·6		
Improvement ascribable to change in Stage distribution of the cases		+5·9	(71)
Improvement ascribable to other causes, e.g., treatment		+2·4	(29)

often neither early nor localized. Not infrequently the earliest symptoms suggest a generalized reaction—malaise, loss of weight and other signs of cachexia, and the subsequent history bears out the assumption that the disease had extended beyond the primary site before the patient sought advice or treatment. Clinical assessment based on a routine pelvic examination lacks the positive evidence that a surgical investigation provides, and is often highly inaccurate.

The records were studied of 133 patients with Stage I or IIA lesions who were treated at the Toronto Clinic and who did not survive a year. Eight patients died of extraneous disease during or immediately following treatment, indicating that even radiotherapy may be dangerous to those who are organically unsound; 4 died from coronary thrombosis, 3 with hypertensive cardiac disease had cerebral emboli, and another died from uraemia, the outcome of an old pyelonephritis with nephrolithiasis.

Eleven of the remaining 125 patients died within a month, and 4 others under three months. Treatment seemed to precipitate a toxic state from which the patient never rallied, and in some massive necrosis became progressive. Induration extended rapidly to fill the pelvis.

Occasionally severe abdominal symptoms developed, sometimes after an interval of several months. Obstruction of small and large bowel occurred, and colostomy, caecostomy and resection did not alter the fatal outcome. Peritonitis developed in 2 cases following resection, and in another case from multiple perforations of over-irradiated bowel. Diarrhoea and melaena marked the rapid deterioration of several other patients.

In recent years operative treatment has been undertaken for some radio-resistant tumours, but in this group with obviously rapidly progressing tumours it presented either an inoperable condition or was followed by prompt recurrence.

Death occurred from uraemia in a number of cases when extension of the lesion or the development of massive post-radiation cellulitis caused obstruction of the ureters. In all but one case when post-mortem examination was made a much wider spread of the malignant process was found than clinical evidence suggested. Several patients died from distant metastases, although the primary lesion appeared to be controlled.

This group of patients presents many instances of an unsatisfactory response to radiotherapy which results not only in necrosis of the local tumour but also of the adjacent normal tissues. It almost suggests that the treatment has had an unfavourable effect on the defensive mechanism of the host, not only regionally but in association with a greater tendency to embolic development. This may indicate that the problem which is often cursorily dismissed as one of radiosensitivity or radio-resistance may have a more fundamental basis.

The Treatment of Recurrent Cancer
(see Murphy and Schmitz, 1956)

Irrespective of the form of treatment, recurrence of the lesion occurs in a disappointing number of cases. This has been the basis for surgical treatment, often of a very radical nature. While it is true that in certain institutions, and in the hands of skilled surgeons of wide experience in this particular field, results have been obtained which justify this routine, this does not apply when such operations are undertaken by those whose experience is limited. It is also true that radical operations have not been very successful when post-radiation recurrence involves the lymph nodes as well as the extra-uterine tissues (Brunschwig, 1959). Therefore, although there is a difference of opinion amongst radiotherapists as to the wisdom of re-irradiation, our experience in Toronto shows that by this means some further control of cancer and prolongation of life can be obtained.

The results of re-treating 137 patients whose tumours were originally classified as Stage I or Stage II are presented in Table VI in which the patients are divided into three groups according to the time between the primary course of treatment and the recognition of recurrent or persistent tumour within the pelvis. In addition to those tabulated, 23 patients have been re-treated in the last five years, and 4 of them are alive and apparently well at the present time.

TABLE VI
Repeat Radiotherapy

Time of Recurrence	Total	5-Year Survival	Per cent Survival
Under one year ..	63	5	9
One to three years ..	39	8	20
Over three years ..	12	3	25
Totals	114	17	15

TABLE VII
Complications Associated with Re-irradiation

Fistula	15
Intestinal obstruction	3
Peritonitis	2
Uraemia-ureteral obstruction	2
Nephrolithiasis	2
Rarifying osteitis	1
Pathological fracture	2
Proctitis (colostomy)	3
Ureteral obstruction (transplant)	4

The dominant problem of recurrence is opportune recognition. The prognostic value of cytology was not evident in this series of patients, and even biopsy sometimes failed to give proof of recurrence when post-radiation necrosis was also present.

In the absence of surface involvement in the vagina deep recurrence was difficult to recognize for two reasons: first, it was often masked by post-radiation fibrosis, and second, it occurred high in the pelvis beyond the reach of the examining fingers.

On the other hand, while it is admitted that clinical judgment in the absence of pathological proof lacks accuracy, and may result in mistaking fibrosis for malignant infiltration, our experience has been that the majority of patients who died passed from an indefinite phase to a positive malignant state only shortly before death. As a matter of fact, 22 patients died within three months, and 38 others within six months, of the second course of treatment. In the majority of these patients treatment had been delayed so long that it did nothing to alleviate the condition.

An inevitable consequence of the re-irradiation of tissues which had already received heavy radiation is the risk of injury which may hasten the death of the patient, or if she survives seriously affect her well-being. Table VII presents the complications which occurred.

It is impossible to dissociate the two factors responsible for some of these complications. For example, in 11 of the patients who developed fistulae it was merely a feature of terminal disease. Only 2 of the other patients are alive at the present; one who has a colostomy has survived four years, and the other with bilateral ureterostomy is living eleven years after treatment.

The 21 patients who survived over five years, or who are living for a shorter period of time, present some interesting features. Two of them, surviving 17 and 20 years respectively, developed chronic nephrolithiasis as the result of ureteral stricture. Two other patients have been treated surgically for second recurrences; one now survives two years after a Wertheim operation performed for a recurrence at the vault of vagina which developed seven years after the second course of radiotherapy, and the other had an exenteration six months ago for a massive recurrence with recto-vaginal fistula occurring three and a half years after re-irradiation.

In reviewing this group of patients and having in mind many others who were not re-treated, one feels that when there is a reasonable possibility of recurrence an exploratory laparotomy should be performed. This alone will allow a thorough examination of the pelvis with biopsy to confirm the diagnosis and the full extent and location of the tumour will be determined. On this basis re-treatment by radiotherapy would be a reasonable alternative to radical surgery, and it might be assumed that a higher salvage rate would result.

THE ULTIMATE FATE OF PATIENTS WITH CANCER OF CERVIX

Although five-year survival is generally accepted as the criterion of the success of treatment much is to be gained by a more prolonged

follow-up study. The ultimate fate of 204 patients who had survived five years after radiotherapy at the Toronto Clinic is the basis for this final study.

Eighty patients eventually died from recurrent tumour, and 21 of the recurrences occurred after the tenth year. Fifty-three of the patients had clinically recognized distant metastases, and it seems likely that post-mortem examination would have added to this number. The longest period which elapsed before a local recurrence appeared was 17 years.

Twenty-seven patients died from a second primary lesion, the commonest site of which, as might be expected, was in the breast. Cancer of the large bowel was the next most frequent tumour, in one case occurring 23 years after the treatment of the cervical cancer. One patient died of cancer of the stomach 27 years after being cured of cancer of the cervix—post-mortem showing the usual extension of such a lesion, the pelvis being clear of all disease.

Seventy-four patients died of extraneous disease in no way associated with either the cervical cancer or its treatment. An interesting speculation is the effect which heavy irradiation might have on the life expectancy of a patient. Apart from the patients who have developed intra-abdominal complications this appears to be negligible, as these patients who mostly died from cardiovascular disease had an average age of 69 years, 24 being over 75 and the eldest 91 years. One elderly patient, who died of pneumonia, at post-mortem was found to have a completely healed pelvic lesion, but had a secondary nodule 4 cm. in diameter in her diaphragm, walled off and obviously quiescent.

Once again post-radiation fibrosis presented not only a diagnostic problem but, alone or in association with recurrent or temporarily controlled cancer, caused ill health which ultimately ended in the death of at least 21 patients. Ureteral transplantation and colostomy, life-saving at other times, failed in these patients because delay had caused too great damage to the kidneys or the state of the abdominal contents presented an impossible surgical problem.

Three patients had pathological fractures of the femur, and osteoporosis was noted in several other patients. There were no cases of leukaemia, but 6 patients developed severe anaemia and in 2 death was attributed to this cause in the absence of malignant disease. Whether or not it is a justifiable conclusion to associate this with previous heavy irradiation is debatable.

Two factors often continue to affect patients who have had radiotherapy for malignant disease. Prolonged observation has shown that the complications which follow radiotherapy present as constant problems as are associated with the surgical treatment of pelvic cancer (Simpson and Spaulding, 1959; Kerr, 1959). The varying length of time which elapses before secondary tumour becomes apparent indicates the individual problem which every cancer patient presents, and suggests the difficulty in deciding as to which form of destructive therapy is most likely to result in either a cure or, what is more often the case, prolonged and reasonably comfortable palliation. Although there is some personal satisfaction in presenting a record of success it still remains a possibility that greater benefit comes from a study of the shortcomings and disappointments of treating any disease.

The author wishes to thank the Directors of the Princess Margaret Hospital; the Directors of the Ontario Cancer Foundation Clinics; Dr. A. H. Sellars, Statistician to the Ontario Cancer Foundation; Mrs. Shirley Gordon and Miss Marguerite Bolster for their help in the preparation of this paper.

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DISCUSSION ON RADIOTHERAPY IN MODERN TREATMENT OF FEMALE PELVIC CANCER

PROFESSOR B. W. WINDEYER (London)

I AM grateful for the invitation to take part in this symposium and to have an opportunity of discussing the influence which developments in radiotherapeutic technique may have in the treatment of cancer of the uterus.

Although the title of this symposium is a wide one, comprising the whole of the female genital tract, I propose to limit my discussion to consideration of treatment of cancer of the cervix uteri. It is in this type of malignant disease that the contribution of radiotherapy is most clearly known and its progress over a period of thirty to forty years has been carefully documented, with sound statistical studies, in reports from centres all over the world.

The earlier volumes of the *Annual Report on the Results of Radiotherapy in Carcinoma of the Uterine Cervix*, were considerably weighted by the results of patients treated in the early years when techniques and dosage estimations of radium application were less precise than in later years, but there has been a very considerable improvement in the overall relative apparent recovery rate from 26·3 per cent in the second report issued in 1938, to 37·3 per cent in the eleventh report issued in 1958.

If a study is based on material from the last five years, when techniques and dosage measurements had become more firmly established, the overall relative apparent recovery rates rose from 36·0 per cent in Volume VI issued in 1951 to 42·8 per cent in Volume XI issued in 1958. When it is realized that these figures relate to many thousands of patients treated there is a significant and steady upward trend.

The reason for this improvement has been discussed at length on many occasions and it appears that it is likely to be due to some combination of (1) differences in the quality of the clinical material, and (2) actual improvement in the results of treatment. It was to be hoped that intensive efforts to improve education in cancer and cancer services would cause a real improvement in the quality of clinical material, but the analysis that has been made of these figures indicates that in this large number of many thousands of cases there is only a slight improvement in the clinical quality of the material, and that it is not the most important factor in the improvement of the cure rate figures. The other factor, actual improvement in the results of treatment, would seem most likely to be due to more meticulous accuracy in the technique of radiotherapy with better dosage estimation, and to improvements in the care and supervision of the patient before, during and after irradiation, with closer attention to rectification of abnormalities in the blood picture and elimination of sepsis. This tendency to improvement is a healthy one and it may be argued that the most immediate objective is for greater attention to be paid to the details of the present basic techniques, so that the results of the average may be brought up closer to those of the centres which are producing the best results. It may be of value however to investigate further the main causes of failure from the techniques which at present are in most general use and to see if there may not be a case for a more general appraisal of the basic techniques of radiotherapy. The tendency at the present time, with few exceptions, is to continue with fairly static techniques of intra-cavitary radium application and to strive to obtain a better effect on extension out towards the pelvic wall and on invaded lymph nodes. To this end much attention has been directed towards improvements in methods of supplementary irradiation of the lateral parts of the pelvis, and experiments with subsequent lymphadenectomy have also been carried out.

The results of radiotherapy of cancer of the cervix uteri treated at the Middlesex Hospital are seen to be somewhere about the average in these collected figures and have been obtained mainly by a technique of intra-cavitary radium application which is not greatly different from

that used in many other centres in this country, modifications being made in the treatment according to individual variations in patients. They must be fairly representative of a good deal of the work which is going on in many centres.

In addition to this form of treatment by radiotherapy alone, an investigation into the value of the treatment of Stage I and Stage II cases by a full course of intra-cavitary radium followed by Wertheim's hysterectomy was started by Margaret Snelling and W. R. Winterton. This work has been reported in the *Thirty-sixth Annual Report of the British Empire Cancer Campaign, 1958*.

So far 90 cases, 51 in Stage I and 39 in Stage II, have been treated by this method. The Wertheim hysterectomy was performed ten to twenty days after the completion of the radium treatment.

In fifty-two of the ninety patients (57·8 per cent), no viable growth was found in the cervix and the lymph nodes were free of tumour. In twenty-two patients (24·4 per cent) viable growth was found in the cervix, but the lymph nodes were free: in eight (8·9 per cent) the cervix contained no tumour cells but the lymph nodes were invaded and in eight (8·9 per cent) tumour was found both in cervix and lymph nodes. Viable growth was found in the cervix in twenty (51·3 per cent) of the thirty-nine Stage II cases but in only ten (19·6 per cent) of the fifty-one Stage I cases. There was therefore persistent viable tumour in the cervix in thirty, or one-third of a series of 90 cases of Stage I and II cervical cancer. The incidence of lymph node involvement was similar in Stage I and Stage II cases.

Perhaps no absolute conclusions can be drawn from these figures. It might be argued that insufficient time had elapsed between the radium applications and the surgical ablation for a true picture to be seen, but they are quoted here as they do tend to substantiate observations previously made that, at least in the apparently early cases, the main reason for failure after radiotherapy is inability to eliminate the local growth in the cervix.

The problem of lymph node involvement in these early clinical stages is numerically of minor importance. There is also the implication that with a more advanced clinical stage, intra-cavitary radium application is less efficient in eliminating local growth in the cervix. It is a reasonable assumption, but one which I have no new figures to support, that in still more advanced cases of Stages III and IV, intra-cavitary radium treatment becomes progressively less efficient for cure of the local disease. In short, my thesis is that the problem of cure of local disease in the cervix has not been adequately solved by present methods of intra-cavitary radium application. In the more advanced clinical Stages III and IV there is the additional problem of regional spread and lymph node metastasis.

The introduction of supervoltage apparatus has undoubtedly been the greatest advance in radiotherapeutic technique in the last decade. The term supervoltage is used to describe radiation of a quality equivalent to that produced by X-ray apparatus working at a million volts and upwards. In practice in this country it means apparatus for routine radiotherapy in the one to ten MeV range.

There are now in Great Britain a number of X-ray machines working regularly at one and two million volts and several linear accelerators working at four million volts and one at eight million volts. There are also a number of cobalt units containing from 1,000 to 2,000 curies of Cobalt 60, which produces a beam of radiation equivalent to that from an X-ray machine working at three million volts. This quality of radiation has several distinct advantages over the conventional X-rays produced in the 200 to 300 kilovolt range, which was previously the routine quality of X-rays used for the treatment of malignant disease. Supervoltage radiation gives a greatly increased depth dose so that a tumour situated at any site in the body can be irradiated to adequate dosage with relatively simple arrangement of treatment fields and without excessive irradiation of overlying superficial tissues. With harder quality of radiation there is more forward scatter and less sideways scatter of radiation. The maximum dose becomes displaced below the surface of the skin so that the skin is relatively less affected than with 250 kilovolt X-rays and there is also a smaller integral or total body dose and less tendency to radiation sickness.

With 250 kilovolt radiation there is a relatively greater absorption of radiation in bone than in soft tissue but with supervoltage radiation the absorption of bone and soft tissue is approximately equal. This means that there is less tendency to bone necrosis with supervoltage, and the shielding effect of bone when attempting to irradiate a tumour underlying it is of comparatively little importance.

A further technical advance in radiotherapy has been the great improvement in methods of suspension and control of movement of radiotherapy apparatus, even the massive and heavy supervoltage machines. This has facilitated greater accuracy in beam direction and the introduction of moving beam techniques, in particular various types of arc rotation.

The object of moving beam techniques is to direct the beam of irradiation so that the tumour is being irradiated throughout each treatment, but the overlying tissues receive a much smaller dose. I believe that rotational techniques have many advantages with supervoltage, and that in irradiation of the pelvis they are particularly suitable to obtain accurate and reasonably homogeneous dose distribution.

The application of supervoltage radiation to the treatment of cancer of the cervix has so far been mainly with the object of obtaining a more efficient method of giving treatment to the sides of the pelvis to supplement intra-cavitary radium techniques, and undoubtedly for this purpose it is a great improvement on the old 250 kilovolt X-rays. I do not think, however, that, despite all the ingenuity that has been used over many years, it is possible to arrange any satisfactory combination of intra-cavitary radium treatment to the centre of the pelvis and external irradiation to the periphery.

Now that it is possible, with this improved quality of irradiation, to deliver an adequate dose with reasonably homogeneous distribution to the whole pelvis without over-irradiation of the superficial tissues, I believe that when supervoltage is used it may be preferable to omit the intra-cavitary radium and do the whole treatment by the supervoltage beam.

At Mount Vernon Hospital we have been carrying out an experiment on these lines in the treatment of some patients with advanced local disease in whom previous experience had shown that it was unlikely that any great measure of success would be achieved by conventional techniques and to see if supervoltage external irradiation was capable of eliminating disease from the pelvis. We are encouraged to think that this thesis is being borne out. Of the 51 (out of 98 patients) who are still living, 44 are considered to have no sign of cancer in the pelvis. It is of course impossible to say if these early results will be lasting, and we have none of them who have so far survived more than four years, but we believe from the evidence we have that this method of treatment is an improvement on what could have been done with intra-cavitary radium and supplementary external irradiation to the parametria, and we intend to continue to use external supervoltage irradiation for the treatment of advanced carcinoma of the cervix. Nevertheless, assuming that this assessment is a correct one, it would not be wise to draw too many conclusions and to treat early cases in this way. Much more controlled work must be carried out on advanced cases and time must elapse to confirm or disprove these observations. We have in local intra-cavitary radium application a proved method of treatment, the best which has so far been developed for the treatment of cancer of the cervix and which has produced a well-established measure of success. It may be that the possible 30 per cent of failure to cure local disease to which I have alluded is a question of the inherent radio-resistance of certain cancers of the cervix, and that it may not prove possible to eliminate them by any method of irradiation. The quality of radiation delivered by a cobalt unit or a 4 MeV linear accelerator is not greatly different from that delivered by standard radium techniques, and, if it were, there is no evidence that alteration of quality of radiation is likely to cause any profound alteration in radio-sensitivity.

I have been asked, however, in this discussion to put forward views on possible future development of modern methods and it seems not unreasonable to suggest that, when much more experience has been gained, methods of external radiation may be developed which will supersede intra-cavitary radium application. It may be heresy to suggest it, but for many reasons it

would be an excellent development if this were so. In most departments intra-cavitary radium applications are the greatest single factor in the occupational exposure of those engaged in therapeutic radiology. There is always a problem in any busy department to keep down to satisfactory levels the exposure of those engaged in making up radium appliances, inserting them in the theatre and even in nursing the patients who have large amounts of radium inserted. In this age of the use of ionizing radiations it is essential that more attention should be given to this problem and, because the whole population will inevitably in the future receive some increase in dose, it is imperative that unnecessary exposure should be reduced wherever possible.

The procedure of making up intra-uterine radium appliances for each case should be altered, and permanently loaded applicators, easily sterilizable by boiling or chemical sterilization, should be adopted wherever this work is carried out in quantity. Other devices for remote handling by personnel must also be adopted, even if it means considerable financial outlay.

In conclusion, it is apparent that the development of supervoltage methods has given some definite advantages in the technique of radiotherapy, and I believe that it has made possible the treatment of some previously untreatable conditions. It has also some disadvantages in that it demands greater accuracy and more careful planning, and the penalty of inaccurate work may be an even greater measure of damage to normal tissues, but these are dangers which can and should be avoided.

Perhaps of greater importance is the fact that there still remain many problems of radiobiology which may have to be answered before further substantial improvement in results is achieved, and it is essential that effort should continue to be directed and intensified in the search for methods of making an early diagnosis of the less radio-sensitive tumours and of means to increase their sensitivity.

MR. C. J. L. THURGAR (Newcastle-upon-Tyne)

WHEN your Committee invited me to make a contribution to this symposium, with particular reference to supervoltage radiotherapy, my immediate reaction was that it is too soon to speak on this subject from my own experience. But, on the principle that Dr. Cosbie has mentioned, that one learns as much from one's mistakes as from one's successes, I think perhaps I might have a little to say. The opening speakers have made so many points with which I am in full agreement that I can pass these over. Following their example, I shall confine what I have to say to carcinoma of the uterine cervix.

My experience with supervoltage treatment of cancer of the cervix dates from 1954. We had a 4 MeV linear accelerator delivered in 1953, and the rest of that year and most of 1954 were occupied by physical measurements and a limited clinical programme. Our figures date from 1955, and so we have no five-year statistics as yet. On the other hand, there has been a good deal of variety of method employed and, for that reason, I have been able to draw some conclusions. In Newcastle, during the war. all of the radiotherapy of malignant disease was transferred to a base hospital 15 miles outside the city. After the war no beds were allocated for radiotherapy in Newcastle and the work is still done in the main gynaecological clinics in the city and the neighbouring town of Gateshead. In the teaching hospital, an average of some 50 cases a year are treated, about the same number or rather less in the Newcastle General Hospital, and the same again or rather more in the Queen Elizabeth Hospital, Gateshead.

The outlook on the treatment of cancer of the cervix is rather different in these 3 clinics. Each clinic is run in collaboration with different radiotherapists of our team, and they too have a rather different outlook, so, although short of large numbers upon which to draw a statistical analysis, we have seen a good deal of variety. At one clinic it is customary to use what I call orthodox radiotherapy—radium insertion with supplementary megavoltage X-rays, and to operate (after a reduced amount of radiation) on the early, the thin and the young, in other words, on the best surgical prospects. I have nothing against that. I think it is quite a reasonable way of tackling the problem. In another clinic it is customary to give full radiotherapy and, in view of the problem of residual cancer

in the cervix, to carry out limited surgery on the operable cases: in other words, a straightforward hysterectomy with minimal removal of cellular tissue. The third unit has varied a great deal over the years in its policy and has changed from radical surgery to radical radiotherapy, and back again to radical surgery, with various mixtures of the two in an investigational spirit which has given a great deal of information. That set-up provides the basis of our experience of supervoltage radiotherapy for cancer of the cervix.

We cannot give long-term results of our own but I should like to quote the figures of Blomfield of Sheffield, which you probably all know. In the period up to 1936, when radium with supplementary conventional X-rays was used, his overall survival figure at 5 years for all the material referred to the Sheffield Radiotherapy Centre was 21·5 per cent, with very little annual variation. When he re-arranged his radium technique by producing applicators with various filters, the survival rate immediately jumped (for the year 1945–1946) to 31·5 per cent, a 50 per cent improvement which was maintained for the next 4 years, again with no variation beyond 1 per cent from year to year. In 1950, he started work with a 2 MeV generator, giving his supplementary X-irradiation with that machine, and again there was a sudden jump in the survival figures from 31·5 to 41 per cent, a rate which has since been maintained and slightly improved. The graph of the results is just like a step-ladder and there can be no doubt that the changes are not due to difference of material but to improvements in technique. Our figures are comparable with Blomfield's although I think on prediction that they will not be quite so good.

Supervoltage machines (including large units of Cobalt 60) make it possible to subject the whole pelvis to any practicable degree of irradiation, without any damage to the skin and without much danger of pathological fracture of the neck of the femur or elsewhere. When I first saw this being done in Houston, Texas, by Gilbert Fletcher and his associates, I was very impressed that they could give as much as 6,000 roentgens to the whole pelvis, perhaps followed by a limited application of radium to the final core. I came back to Newcastle with the intention and the hope of doing the same thing. I felt that the 4 MeV linear accelerator, which has definite though perhaps not great advantages over the cobalt unit, would let us get away with it, so to speak, and in general we have and we can give those large doses to the whole pelvis in safety. But there are circumstances when we cannot. One can give up to the 6,000 roentgens I mentioned, the maximum pelvic dose, to most people but it is not safe to do so after surgical exploration or excision or after previous pelvic inflammatory disease. I myself admit to a surgical bias and I should much prefer to see a cancer removed, other things being equal, but we are only now beginning to learn just which cases would be better submitted to less radiotherapy and more surgery. One must give a major regard to grading, but, as Dr. Cosbie has said, there is no satisfactory method of grading; we have to fall back on "differentiated" and "undifferentiated". Our tendency would always be to use surgery as the major weapon of attack for the undifferentiated cases. The preliminary radiotherapy has to be given at a time and also in a dosage which has relation to the surgery which is to be performed afterwards.

As regards complications, in the first 200 cases treated with megavoltage therapy in Newcastle there were 10 instances of bowel injury in the first 100 cases, but only 2 in the last one hundred. Of those 10 cases, 5, probably 6, were serious, the others more minor. With increasing experience of the method the number of such injuries has been falling off. Bladder and ureteric injuries and kidney damage all appear rather later, although they are not apparent unless one is looking for them all the time; they have not in the main worried us so much where megavoltage treatment has been used as they did when intra-cavitary radium was pushed to its limits.

No doubt megavoltage therapy will in the future completely replace conventional therapy as we have known it in the past. I do not myself, however, feel that as yet we are in a position to replace intra-cavitary radium by megavoltage therapy, at any rate for the earlier and operable cases. It is true that by rotational and other

techniques and by using small fields, one can limit the high dosage into a limited volume comparable to that treated with radium, but I do not feel the time has yet come to do that. We have attempted to do it in those late cases or recurrences where there is, say, a known node on the pelvic wall, revealed at laparotomy. Our experience has been that, while giving immediate or early relief of pain, the effects have not been lasting. Palliation by wide fields and with lower dosage is one of the finest features which megavoltage therapy offers. One can treat quickly, safely and in reasonable comfort patients who would certainly not tolerate such palliative treatment by conventional X-rays; that, no less than the curative aspect, is to my mind one of the greatest contributions the new developments in radiotherapy techniques have to offer.

MR. S. A. WAY (Newcastle-upon-Tyne)

I HAVE had the opportunity in the last many years to look at much histological material removed from patients who have undergone radiotherapy for cancer of the cervix. Some of this includes supervoltage X-ray therapy cases, in whom there is to my mind one striking feature, namely, the degree of endarteritis which is seen in both the cervix and the parametrium. This appears very quickly after supervoltage X-ray therapy, but is not seen to such marked degree nor nearly so quickly after intra-cavitary radium. Since the quality of radiation from the 4 MeV linear accelerator and from radium is much the same, I can only assume that the bulk of tissue must play some part.

One patient died some 5 months after supervoltage therapy with local recurrence and a fistula into the bladder caused by growth; the portion of cervix with no residual tumour showed extensive vascular changes and no recognizable living tissue. Another woman required exenteration for local recurrence 14 months after receiving 5,000 roentgens for an early Stage II lesion; the parametric tissue showed marked hyaline change, the cervix itself presented obliterated blood vessels and foci of active carcinoma; a lymph node from the parametrium showed active cancer but no change in its structure. Of all the many nodes I have seen removed after supervoltage treatment, none has presented any damage whatsoever. A third case, aged 36 years, received 4,800 roentgens over a period of 8 weeks in 1956 for a Stage I carcinoma. Some 5 months later, although the cervix looked perfectly healthy, operation was decided upon as the original biopsy had revealed a type of carcinoma which in our experience is seldom cured by any form of radiotherapy. Histological examination of the cervix after removal showed that the cancer persisted and that there was little or no change from its original appearance. The patient remained well until December, 1958, when she presented with acute intestinal obstruction and peritonitis. At laparotomy the peritoneal cavity contained free faeces; two feet of lower ileum, the whole caecum and half the ascending colon had been converted into a cartilaginous mass, with multiple fistulae. Histological study of the resected bowel showed gross endarteritis and tissue necrosis. She recovered from this operation of gut resection but 6 weeks later developed severe haematuria from necrosis of the bladder. Communications arose between bowel and bladder, and a hole appeared in the abdominal wall through which poured both urine and faeces until she died. Another woman also developed a leakage of urine and faeces through the abdominal wall but we have been able to help her by means of surgery.

Let us get this chamber of horrors into proper perspective. Of 130 cases treated with supervoltage therapy, there have been 8 instances of major bowel disasters, ranging from stricture with the need for permanent colostomy up to complete gangrene of the entire large intestine and the distressing case of perforation already described. This is an incidence of about 6 per cent. We have had some bladder troubles but they have not been so disastrous as those affecting the bowel. I am the last person to suggest that supervoltage X-ray therapy has no place but we must not run away with the idea that if we put more noughts in front of the volt sign and more noughts after the £ sign it will all look very impressive and is bound to do some good! To me the future control of

cancer of the cervix lies in very much earlier diagnosis, however it be treated, because we have now exhausted the possibilities of surgery and just about those of radiotherapy too.

DR. I. CHURCHILL-DAVIDSON (London)

OXYGENATON IN RADIOTHERAPY

FIFTY years ago Schwarz (1909) first observed that ischaemia produced by local pressure increased the resistance of human skin to damage by X-rays. Subsequent work showed that small animals and tumour grafts were protected from radiation damage if irradiated while deprived of oxygen. Clinical radiotherapists have also long been aware that tumours with a good blood supply tend to be more radio-sensitive than similar tumours growing in scarred or otherwise ischaemic regions. Little practical use was made of this knowledge until Gray and his colleagues (1953) demonstrated that in a wide variety of animal and vegetable tissues there was a general relationship between the sensitivity of all living cells to damage by X-rays and the concentration of oxygen around them at the time of irradiation. If a cell is deprived of a normal oxygen supply its radio-sensitivity may be reduced by as much as two-thirds, but will not be greatly increased in the presence of excess oxygen.

It has now also been shown (Thomlinson and Gray, 1955; Churchill-Davidson, Sanger and Thomlinson, 1957) that in nearly all types of neoplasm there are likely to be cells which are deficient of oxygen, due either to inadequate local circulation, the particular pattern of tumour growth or both factors. These cells may survive the largest dose of X-rays which a person can tolerate, and lead to recurrence of the growth.

At present the only practical way of increasing the oxygen concentration around tumour cells is for the patient to breathe oxygen, and further, it seems likely that, owing to the circulatory conditions, a sufficient increase will be obtained in most tumours only by using oxygen at high pressure. This involves the patient being enclosed in a pressure chamber during irradiation and gives rise to many technical and physiological problems.

At St. Thomas's Hospital in 1954 we started an investigation into the effects of irradiating tumours in patients breathing oxygen at 3 and later 4 atmospheres absolute. One of the prime difficulties to be overcome was the production of convulsions known to occur in divers breathing oxygen at this pressure. It was believed, and is now established, that these can be prevented by the use of a general anaesthetic, which has the added advantage of avoiding claustrophobia and ensuring that the patient remains still during treatment.

From the first eight patients who were treated, evidence obtained from microscopic examination of the irradiated tissues strongly suggested that the addition of oxygen produced an enhanced effect (Churchill-Davidson, Sanger and Thomlinson, 1955). Subsequently, 72 patients who were considered to have little, if any, chance of cure by conventional radiotherapy have been treated. As a comparison 15 similar patients have been treated while breathing air at atmospheric pressure.

The results are shown in Table I. Although the number of patients treated is too small, and the time that has elapsed too short, to permit accurate assessment, the results have continued to be encouraging in that of the 72 cases treated in oxygen 13 are alive without any evidence of growth for periods up to 3½ years, and in 28 cases there has apparently been complete

TABLE I
Results of Treatment

Radiation Therapy with O_2		Control Radiation Therapy
13/72	Alive and well. No evidence of growth	0/15
28/72	Resolution of primary and secondary growth in irradiated area	0/15

Tumours of larynx and pharynx (27); tongue, tonsil and palate (19); bladder (11); bronchus (10); bone (7); uterine cervix and vagina (4); oesophagus (3); brain (2); lip (1); adrenal (1); parotid (1) and soft tissue (1).

Preliminary results, 87 cases, June, 1955–June, 1959.

resolution of primary and secondary growth in the irradiated area. None of the 15 cases treated in air have even shown complete regression of growth in the irradiated area.

Only 4 gynaecological neoplasms have been treated. One further case which was originally thought to be a carcinoma of the ovary, recurrent after surgery, subsequently proved to be a neuroblastoma of an adrenal gland. Three patients had carcinoma of the cervix or vaginal vault and 1 patient had a carcinoma of the posterior vaginal wall. In all cases the growths were very advanced and extended to the side walls of the pelvis. One case out of the four, the patient with carcinoma of the posterior vaginal wall, responded extremely well, and is alive and well without evidence of growth 2 years after treatment.

In conclusion, although this type of treatment is still in the experimental stage, there is reason to hope that the use of oxygen in conjunction with radiotherapy may lead to a considerable improvement in the present cure rates, especially in earlier cases. Meanwhile, it is important to note that Garcia (1958) has shown that the 5-year survival rate of patients with carcinoma of the cervix treated by irradiation was markedly worse if they were anaemic at the time of treatment. It would, therefore, seem advisable to transfuse such patients if curative radiotherapy is to be attempted.

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THE PLACE OF OXYTOCIC DRUGS BEFORE THE BIRTH OF THE CHILD

BY

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THIRTY years ago a medical student failed in his final examination if he advised the use of ergot to stop haemorrhage in the third stage of labour —and indeed it never was used at that time. Today all are agreed that it is better to be alive, even with the placenta retained, than to be dead, albeit with the satisfaction that it has been removed.

Few also will actively dispute the practice of giving prophylactic ergot as the baby is being delivered, though personally I believe this treatment should be reserved for those cases where an inert uterus, and therefore haemorrhage, may be expected. If the management of the third stage of labour is correct, then nearly always the placenta is expelled without much blood loss. Therefore, in the normal, healthy woman, who is not exhausted, I see no reason for the routine administration of ergot at the end of the second stage.

We now come to what will surely provide less agreement—this matter of pitocin.

It was just over half a century ago, 1906, when Sir Henry Dale for the first time demonstrated the oxytocic principle in the extract of the posterior part of the pituitary gland. Three years later Blair Bell (who was to be the first President of our College) was able to write on its clinical application in obstetric practice. In his paper he used these words "I am inclined to think that in the future we shall rely on infundibular extract to produce contraction of the uterus in many serious complications and difficulties". Continuously since that time attempts have been made to assess the clinical value of the extract. Adverse reports, however, were constant in their appearance and investigations were terminated prematurely as the direct consequence of discouraging results or even because some disaster had occurred. This unsatisfactory state of affairs was largely due to the fact that until relatively recent times the preparations were impure and the standardization and dose anything but exact. In the last decade, however, the picture has changed with the appearance of what is usually termed "The Pitocin Drip". In the American Medical Press especially, and more recently in the British Journals, have appeared article after article which, almost without exception, describe the use of the pitocin drip in the induction of labour, in the treatment of hypotonic uterine inertia in labour, and in other less common conditions. These publications include series of hundreds, and in some instances thousands, of cases in which it would seem that pitocin, or an equivalent synthetic preparation, administered by the method of an intravenous drip has been successful, and almost complication-free, in the great majority of cases.

One of the most comprehensive surveys is that of Hellman, Kohl and Schechter (1957). In this paper a review is made of the use of the pitocin drip in no fewer than 5,656 instances (9·0 per cent) of 63,276 deliveries in ten large hospitals. In two hospitals the use of pitocin preceded the birth of the baby in over 20 per cent of cases. There were no maternal deaths in

the series; one case of uterine rupture was recorded. In the author's words, the perinatal mortality was gratifyingly low. The majority of papers published seem to record a consistently high rate of success, and absence of risk to mother or child, in the use of pitocin either to induce labour or to remedy the state of hypotonic uterine inertia.

With a natural anxiety to do all that is best for our patients a somewhat belated start was made in the use of the pitocin drip in the Obstetric Department of St. Thomas's, Lambeth and the General Lying-In Hospital. Over the last three years this technique has been employed, exactly as advised by those with great experience, in 60 cases (0·6 per cent) out of 10,000 deliveries. This is admittedly a very small series, but the fact that the cases were selected may be of importance when comparison is made to the practice of other units or departments where the order to "set up a drip" is issued 20, or even 40, times as frequently.

The cases are consecutive, none has been omitted, and the patients represent in age, parity, social class and all other criteria that are now regarded as important, exactly a cross-section of the in-patient population of the departments. The indications for the use of the pitocin drip were to induce labour in 52 women and in the treatment of hypotonic uterine inertia in 8 cases. In 6 of the latter the result upon inertia was noted to be "successful" but 2 of the babies were stillborn. In the 2 "unsuccessful" cases the labour was terminated by abdominal section and both babies survived.

The indication for induction of labour was either pre-eclamptic toxaemia (44 cases) or intrauterine death or a severe congenital deformity of the foetus (8 cases). In two-thirds of these cases the result was, statistically at any rate, satisfactory in that labour started and the delivery of a healthy baby was accomplished. What does not appear on any statistical survey are such items as the discomfort suffered by the woman, the anxiety of her attendants, or the peculiar behaviour of the uterus in the 3rd stage of labour. However, to return to facts. In no less than one quarter (13 cases) of these women severe uterine inertia occurred necessitating delivery by Caesarean section on 3 occasions. There were 5 instances of severe post-partum haemorrhage due to uterine atony and manual removal of the placenta was twice performed. As the result of the inability of the woman, through apparent exhaustion, to make the necessary expulsive efforts, labour had to be completed no less than 13 times (one-quarter of the cases) by the use of the obstetric forceps. There was one maternal death from amniotic embolus and many anxious moments in a few other cases. Especially was this so in one woman, who after the start of the pitocin infusion in the weakest solution promptly developed a tonic uterine contraction, following which the foetal heart was not heard. With an experience such as this it is not surprising that some of us view the pitocin drip with some suspicion.

An examination of the last 2,000 consecutive reports on Maternal Deaths in England and Wales showed that mention was made of the use of pitocin on only 40 occasions. The first point of interest is that no record is made of death following—not necessarily due to—the use of the pitocin drip (9 cases in all) before 1955, which is about the time, probably, that the wider use of this technique became established. In the remaining 31 cases pitocin had been administered by intramuscular injection. That it is possible that sudden death from amniotic embolus may be related to the violent uterine contractions following pitocin injections is suggested by the case already mentioned in the St. Thomas's series and by 2 others from the Confidential Records where this diagnosis was arrived at after post-mortem examination. In 5 additional cases sudden collapse and death occurred. The cause of death is unknown though the clinical picture might well again have been that of amniotic embolus. (It is not claimed that this suggestion is original. The association has already been noted and perhaps the most impressive evidence is that contained in the June issue of the *American Journal of Obstetrics and Gynecology*. There Barno and Freeman (1959) note 15 cases of amniotic embolus and in 7 of these death followed the use of pitocin. They write "It is safe to say there is an association".) One case of uterine rupture occurred as a direct result of the administration of pitocin and in 3 others the condition was diagnosed

after a varying interval had elapsed following the injection of the drug. In most of the remainder of the cases in which death occurred and in which intramuscular injections of pitocin had been given either immediately prior to the onset of labour or during labour, a definite pattern of events becomes clear. Uterine inertia occurred sooner or later. If this happened in the first stage treatment was often by Caesarean section, if in the second stage delivery was completed by the forceps, and if in the third stage death by what was described as "intractable haemorrhage". (It should be mentioned that no case was thought to have been suffering from afibrinogenaemia.)

It is quite certain that pitocin is still, and frequently, administered by intramuscular injection. By this method it is possible that the needle can enter a small vein, an accident that cannot be avoided but which would lead to the uterus being subjected to the sudden stimulus of a relatively large dose of the substance. This Congress would render no disservice to the community if it declared its complete condemnation of the practice of administration of pitocin by the method of repeated intramuscular injections.

Of the 9 cases of death associated with the use of the pitocin drip one patient died as the result of peritonitis following Caesarean section. This operation was performed on 4 other women, twice when the drip had failed to start labour in cases of alleged postmaturity, and twice when the uterine contractions were so strong as to lead to the diagnosis of foetal distress. Death occurred immediately after the operation and in 2 cases was thought to be due to shock (possibly again amniotic embolus) and in the remaining 2 to "massive post-partum haemorrhage as the uterus refused to contract". In the last 2 cases the drip was set up in an attempt to treat uterine inertia. In both collapse and sudden death, stated to be due to "shock" (again possibly due to amniotic embolus) followed soon after the administration had begun.

Admittedly the series of deaths abstracted from the Confidential Reports is small. It is a minute fraction of some 4 million births and a small fraction of some tens of thousands of women who must have received the pitocin drip during the last four years. Be this as it may, there remain those of us who, by their appreciation of the safety of childbirth and who in their practice of midwifery have true contact with their patients, have other views. And I would at this point express with maximum emphasis complete disagreement with the words used by Dr. G. W. Theobald in the Advance Programme. He writes: "The physiological drip requires no supervision other than given to all women in labour. It can be used in any patient who is fit to go into labour, is efficient, and is so safe that it can be used in a cottage." While I disagree with every word quoted above, I believe that the last 10 words advise a procedure that is positively dangerous. All who were responsible for the patients in the small series of cases just analyzed from St. Thomas's and allied units will never forget the anxiety that inevitably accompanies the decisions that have to be made in the diagnosis of foetal distress or in the necessity for Caesarean section, the wearisome and constant observation of a pitocin labour, the forceps operation so often necessary in a tired woman whose uterus had begun to show signs of secondary inertia, the subsequent management of post-partum haemorrhage or the performance of a manual removal of the placenta and, finally, in too many instances the almost helpless observation of the slow return to life of the baby born in white asphyxia. It is by these and similar points, and not by statistics, that we should assess success or failure of any procedure such as the pitocin drip.

We all wish and try to keep abreast of the times, but some of us have had in the past or have now, and I venture to surmise always will have, not only no familiarity with (to quote Dr. Hellman) but an actual suspicion of this substance Pitocin.

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DISCUSSION ON THE PLACE OF OXYTOCIC DRUGS BEFORE THE BIRTH OF THE CHILD

PROFESSOR J. CHASSAR MOIR (Oxford)

SOME observations on the action of oxytocic drugs on the human uterus during labour will be presented by Mr. M. P. Embrey. I shall, therefore, restrict myself to a brief account of the history of this subject.

Investigation of the behaviour of the human uterus in labour largely depends on the use of mechanical recordings. These have been made over the past 60 years and more. Some workers have used an internal method, and others an external method involving the application of some form of recording apparatus to the pregnant abdomen. In 1927 Bourne and Burn described their very practical intra-uterine method by which a small, flat bag was slipped between the foetal membranes and the uterine wall. This was a method which much appealed to me, and which I later adapted to the puerperal uterus, thus enabling recordings to be made of the action of drugs such as ergot which, if given during labour, were known to be dangerous to both mother and foetus.

In recent years there has been renewed interest in this work, largely because of the perfecting of various forms of apparatus which could be applied externally; amongst the many names which should be mentioned in this connexion are those of Lorand of Budapest (1947), Embrey of Oxford (1955), and Smyth of London (Nixon and Smyth, 1957). It is perhaps open to doubt whether the results obtained by the external method are quite as reliable as are those obtained by the intra-uterine bag method already mentioned, or by the amniotic-puncture method described by Alvarez and Caldeyro (1950) and by Stallworthy and Williams (1952). Qualitatively they are very similar; quantitatively they may, or may not—according to the faith of the worker—be entirely comparable. Be this as it may, the external method has the merit of simplicity and the advantage of ease of application.

This brings me to my first point. I would make a strong plea that any oxytocic drug administered during labour should be controlled by a graphic recording of the uterine action. Only by so doing can the obstetrician in charge be assured that over-strong or over-frequent uterine contractions are not taking place as the result of the medication. The alternative of employing an assistant to sit by the patient with his hand registering the uterine activity, is, of course, possible; but it is common experience that assistants who are, as it were, "press-ganged" into hours of this service are far from reliable.

Looking back on the history of oxytocic drugs administered during labour, one recalls the early use of crude ergot powder to expedite "lingering labour". This use was proclaimed by Dr. John Stearns in his famous letter published in 1808; and soon after—to judge from the medical writings of the time—the practice became widespread. But before very long the danger of the drug became apparent; babies were stillborn because of intra-uterine asphyxia, and mothers died from rupture of the uterus. The *pulvis ad partum* was renamed the *pulvis ad mortem*. The use of ergot became restricted to the post-partum period (Moir, 1955).

Perhaps an apology should be offered for repeating this well-known story; but it is well to remind the younger members of the audience that all oxytocic drugs administered during labour are potentially dangerous. And if further justification is needed it is to be found in the story of the obstetrical use of posterior pituitary extract.

When in 1906 Dale observed, quite fortuitously, that a cat's uteri became tensely contracted after the administration of pituitary extract, a discovery was made the importance

of which even he could scarcely guess. Before many years had elapsed the use of posterior pituitary extract became established as a means of expediting labour, just as ergot had been a hundred years before. Once again there followed the same blind enthusiasm, the same mistakes, and the same recriminations. It was found that pituitary extract, no less than ergot, could be deadly when administered during labour.

We must now turn to the work conducted by Burn and Dale (1922) in the National Institute for Medical Research. A reliable method of standardizing pituitary extract was devised. Commercial samples were tested; and it was not altogether a surprise when it was found that the preparations then on the market varied greatly in activity. The difference in some cases was as much as eighty-fold. Imagine then the plight of a patient receiving such an outrageous dose. Or think by analogy, of the state of a child who might be given 80 ounces of castor oil when 1 ounce was intended!

With commendable speed legislation was introduced. Soon only standardized preparations were permitted for sale, and the result was the International Unit dosage which is now clearly marked on every ampoule of the extract. The terrible happenings previously associated with pituitary administration, and which I as a student heard discussed on many occasions by my chiefs, now virtually ceased to exist.

A further advance was made when in 1927 Bourne and Burn were able, after a carefully controlled clinical investigation, to give an authoritative ruling on dosage. They stated that a dose not exceeding 2 International Units by intramuscular injection was, in the case of a normally acting uterus, a useful stimulus and one which was unlikely to be dangerous in its effects. The days of massive pituitary dosage—for example, 1 ml. (10 units) in a single injection—were now over. These large doses were entirely condemned, not only because of the danger to the foetus and the risk of uterine spasm or even rupture, but also because of the harmful effect on the action of the heart muscle—pituitary shock as it came to be called.

But although pituitary therapy had been placed on a more rational basis, many observers continued—and with reason—to doubt its safety. Even with moderate dosage the action of the extract is admittedly erratic, and a supposedly safe dose may sometimes induce over-powerful and over-frequent contractions. Here I might quote an example. A few weeks ago a patient in my charge had a dose of pituitary extract administered by intramuscular injection. Only two units of oxytocin was used; but the uterine contractions, previously sluggish, became so strong and so frequent that the foetal heart slowed dangerously with each contraction, then slowed continuously, and finally ceased before the baby could be extracted.

The most recent advance was made when in 1943 Page, and in 1948 Theobald in this country, advocated the giving of a very dilute solution by intravenous "drip". This method has the great advantage that the observer can control the administration according to the effect required.

Obstetrical literature is now full of reports of the use of intravenous oxytocin "drip", and it will doubtless be the chief topic of discussion in this symposium. That the uterine contractions can be increased at will is incontrovertible; that the contractions so induced really shorten labour if oxytocin is administered early in the first stage is less certain; that the method is reliable for induction of labour when labour is not already imminent is still more a subject of controversy, which I hope will be settled today.

My brief historical survey will have been meaningless if it has not served to point out the potential danger of all oxytocic drugs administered during labour. Here, I might mention that there is a considerable difference between stimulating a uterus that is known to be unusually sluggish, and stimulating a uterus that is already acting normally or even acting more briskly than usual. The latter practice is certainly dangerous and, as the late Joseph DeLee once remarked in this connexion, "a streamlined labour is as safe as a streamlined parachute".

One more matter I would mention. It is generally assumed that the obstetrician need only interest himself in the oxytocic fraction of posterior pituitary extract—that fraction which, by the Parke Davis firm, is termed Pitocin; and which has been, by remarkable chemical ingenuity, successfully synthesized by the Sandoz firm and

marketed under the name of Syntocinon. In truth, matters are not so simple. In 1934 and again in 1944, I was able to show (and other workers have subsequently confirmed the observations in varying degree) that the response of the human uterus to the oxytocic and vasopressor fractions depends on the physiological state of the organ at the time of the administration. Thus, the non-pregnant and the early pregnant uterus respond more readily to the vasopressor fraction. If, however, the uterus in early pregnancy is already actively aborting its content, it will respond to both fractions. It is only towards the end of pregnancy that the effect of the oxytocic fraction becomes so very conspicuous. These effects appear to be exactly reproduced when the naturally occurring oxytocic fraction is replaced by the synthetic preparation now available.

Finally, a word about the modern purified alkaloid ergometrine, and its semi-synthetic cousin which is now marketed under the proprietary name of Methergin. So far as I know, no one has yet attempted to equate the action of a dilute intravenous "drip" of either of these substances with that of a similar oxytocin drip. The reason is that all ergot alkaloids tend to induce a series of rapidly occurring uterine contractions which are dangerous to the foetus. That is not to say that a similar effect may not be obtained by an overdosage of oxytocin.

There is however this difference between the two classes of oxytocic substance. Although dangerously strong and over-frequent contractions can be induced with oxytocin, the uterus will soon revert to more normal activity after the discontinuance of the administration. A comparable action induced by an ergot alkaloid will, however, tend to continue for many minutes before subsiding. There is therefore no justification to experiment with the more potentially dangerous drug in the presence of a viable infant. If, however, the foetus is known to be dead the opportunity may well be taken to observe the effect of a dilute ergometrine "drip", particularly with regard to its suitability for inducing labour. Investigations to this end are now proceeding, but it is as yet too early to report on the result.

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Mr. G. W. Theobald (Bradford)

I am extremely grateful to Mr. Wrigley for drawing attention to the dangers of the pharmacological oxytocin drip. No amount of control, whether human or mechanical, can make a high concentration of oxytocin in the drip safe. There is absolutely no danger at all associated with the physiological oxytocin drip, and seeing that it is physiological it can be given to all patients considered fit to go into labour and requires no supervision of any kind other than that given to all women in labour. Mr. Wrigley has, in his own inimitable way, made this danger crystal clear.

It is a privilege to follow Professor Chassar Moir, who in 1932 proved that the water-soluble fraction of ergot had a powerful oxytocic action, and subsequently with Dudley (1935), isolated ergometrine. He later showed (1944) that the physiological state of the uterus determines its response to post-pituitary extract. He has discussed with authority the changing views concerning ergot during labour and the puerperium. I will merely make one observation *en passant* and that is that the routine intravenous or intramuscular injection of ergometrine, either when the head is crowned or the anterior shoulder is about to be delivered, will probably kill an unsuspected twin. We lost two in this

way last year and my colleagues and I prefer the routine intramuscular injection of 2 units of oxytocin as the head is crowned. This procedure has halved our incidence of post-partum haemorrhage and of manual removal of the placenta.

Before discussing the physiological use of oxytocin it is worth observing that "sweeping" and rupture of the membranes, and dilatation of the cervix are powerful oxytocic agents and that all the purgatives have an oxytocic action of which the most potent is castor oil (Dawson and Mathie, 1959). Further, many of the depressant drugs such as morphine, hyoscine, pethidine, chlorpromazine and the barbiturates exert a powerful indirect oxytocic action, and indeed morphine causes direct increased uterine activity (Caldeyro-Barcia *et al.*, 1955). We use these drugs very freely and add either pethidine or chlorpromazine (or both) to the drip bottle. We believe that they not only relieve pain but shorten labour, depress factors which provoke inco-ordinate uterine activity and often make an irregular foetal heart regular. It is probably only in cases of premature labour that such depressant medication is potentially dangerous.

Quinine is a powerful oxytocic drug but does sometimes cause death of the foetus, and for this reason cannot be recommended for inducing labour now that we have better means at our disposal. Quinine 10 gr. q.i.d. or quinine 2 gr. added to oxytocin in the drip bottle, is useful (and usually succeeds) in inducing labour after the foetus has died. Where this treatment fails its success can be facilitated by a single oral dose of 0·25 mg. ergometrine. The ergometrine drip is not without circulatory risks.

Whereas ergometrine has proved its value at the end of labour, oxytocin, which is not a drug except when used in pharmacological amounts, has been used to induce labour, to enhance ineffective uterine activity, to prevent post-partum haemorrhage and to prevent mammary engorgement. Fifty years ago the obstetrician avoided operative interference because he dreaded puerperal sepsis. The sulpha drugs and the antibiotics have virtually abolished puerperal sepsis and the blood transfusion services have markedly reduced the dangers from haemorrhage. Operative interference has in consequence increased and the desire to conserve foetal life has prompted obstetricians to prevent prolonged labour. The rival procedures used to this end are Caesarean section on the one hand and amniotomy and the oxytocin drip on the other. Some regard Caesarean section as too often being a lazy way out of a difficult situation and in any case a brutal and mutilating operation with ethical complications.

Before adumbrating the use of oxytocin in labour, without which amniotomy would be impracticable, I would stress the point, which is often overlooked, that if all our patients were healthy and well-nourished and had themselves been born to healthy and well-nourished mothers, there would be little need for either Caesarean section or induction of labour. Better nutrition has almost eliminated serious degrees of contracted pelvis and I would suggest that still better nourishment, smoke abatement, better housing conditions and a saner, healthier and more disciplined environment would almost eliminate premature labour, postmaturity, accidental haemorrhage and much of the so-called "toxaemia" of pregnancy, together with inco-ordinate uterine activity.

Prematurity, directly or indirectly, is the main cause of perinatal mortality. The premature birth rate in England and Wales is 7, in Scotland 5, in Holland 3·5 per cent, and in a healthy farming community in Finland, as well as in Social Grade I women in Aberdeen, not more than 2 per cent. One further point. In cities in southern England, where the obstetric and perinatal problems are less pressing, between 70 and 80 per cent of all confinements occur in hospital, whereas only 40 per cent or less of deliveries occur in hospital in some of the most difficult areas in the Midlands and in the industrial North. So much for planning. At Bradford we delivered just under 3,000 women in 1958 with only 51 lying-in beds, over 700 of the patients going home within 48 hours or less after delivery. This was only possible because we were able to resort freely to induction of labour in order to clear the first stage ward and to make the best use of antenatal beds.

Earlier this year (Theobald, 1959) I reported the results obtained from induction of labour at Bradford during 1957. The combined figures for the two years 1957 and 1958 are here presented:

During these two years 5,581 women were delivered of 5,710 babies. Induction of labour was done on 1,482 women, 27 per cent of all deliveries. These patients have been divided into four groups: (1) those induced before 38 weeks; (2) those induced between 38 and 40 weeks; (3) postmature women; and (4) all induced patients who were given an oxytocin drip.

Group (1) consisted of 48 women (3·27 per cent) who elsewhere would be called pre-eclamptics and most of them were emergency admissions. There is not likely to be any difference of opinion concerning their treatment. Seeing that less than 50 women, over a period of two years, had labour induced or Caesarean section performed before the 38th week because of toxaemia, it is clear that the virtual elimination of eclampsia and pre-eclampsia in the city of Bradford has not been achieved by frequent resort to the induction of premature labour.

Table I shows the methods of delivery and reasons for inducing labour in the 754 patients (51 per cent) in Group (2). The most important indications for induction were hypertension, either alone or associated with proteinuria and oedema, high head, and a minor degree of cephalo-pelvic disproportion. The gross perinatal mortality for this group was 18 or 2·4 per cent, and the corrected figure was 11 or 1·4 per cent.

Table II indicates the methods of delivery of the 680 patients (46 per cent) in Group (3). The figures for the two years have not been combined, but are presented separately to show the remarkable consistency of the numbers in each category. The gross perinatal mortality for this group was 5 or 0·7 per cent, and most of those deaths were avoidable.

Table III gives the most important facts concerning the 295 women in Group (4) who were given an oxytocin drop which was run at between 20 and 40 drips per minute. It is clear that 88 per cent were delivered when not more than 5 mU/min. of oxytocin were given (1 unit in 500 ml. drip bottle) and that 33 per cent received less than 2·5 mU/min. ($\frac{1}{2}$ unit in bottle) of oxytocin. Further, many of the women who were given between 5 and 10 mU/min. (2 units in the bottle) of oxytocin, received it on the first or second day without effect, and were ultimately delivered when less than 5 mU/min. of oxytocin was delivered by the drip.

Table IV gives comparable information concerning the 110 women who were given an oxytocin drip in 1958 because of inadequate labour which had started spontaneously. In this group 48 per cent were delivered when not more than 2·5 mU/min. of oxytocin were given, while only 6 per cent were at any time given more than 5 mU/min. of oxytocin.

The points I would like to stress are:

(1) No sensitivity test is of any value in determining whether or not it is advisable to induce labour. The ripeness of the cervix is the sole practical criterion. If the need for induction is thought to be urgent it must be performed whatever the state of the cervix.

(2) I have arbitrarily designated any drip which delivers more than 5 mU/min. of oxytocin as pharmacological, and have deprecated ever giving more than 10 mU/min. of oxytocin. Without starting an academic discussion I would affirm, for practical reasons, that those who advocate the contrary view do infinite harm to the method. More than 60 per cent of all hospital deliveries in England and Wales take place in non-teaching hospitals, and it is physically impossible in such institutions to provide doctor, student, midwife or pupil to sit by the patient's bed. Conditions are still more difficult in many parts of the Commonwealth. It means that those who advocate a pharmacological drip wish to confine it to the teaching hospitals, many of which are quite uninterested in it. I want it used in every cottage hospital throughout the world. Even if it could be shown that the pharmacological drip did effect delivery slightly quicker than the physiological drip (and no such figures have been presented) it would still be undesirable to advocate its use. We have used the physiological oxytocin drip in Bradford for 11 years, and during the whole of that time no harm has come to a single mother, notwithstanding the fact that all these women have been relegated to the care of the nursing staff after the drip has been started. It is physiological and therefore safe, and we believe it is as efficacious as the potentially dangerous pharmacological drip.

TABLE I

Methods of Delivery and Reasons for Inducing Labour. Group (2): Women 38 to 40 Weeks Pregnant. 1957 and 1958

	Total Numbers	Number of Cases of											
		Oxytocin Drip	Spontaneous Delivery	Caesarean Section	Forceps Extraction	Hypertension Alone	H+P	H+O	H+P+O	A.P.H.	Rhesus Antibodies	Free Head +	Routine
Primigravidae	270	72 (26·6)	189 (70·0)	14 (5·2)	67 (25·0)	147 (54·0)	39 (14·0)	20 (7·0)	11 (4·0)	11 (4·0)	2 (0·7)	20 (7·0)	14 (5·2)
Gravidae 2 and 3 ..	342	66 (19·0)	313 (92·0)	19 (5·6)	10 (2·9)	149 (44·0)	26 (7·6)	9 (2·6)	7 (2·1)	12 (3·5)	22 (6·4)	82 (24·0)	23 (6·7)
Gravidae 4 and 4+ ..	142	38 (27·0)	133 (94·0)	6 (4·2)	3 (2·1)	51 (36·0)	3 (2·1)	3 (2·1)	0 (0·0)	13 (9·2)	17 (12·0)	33 (23·0)	9 (6·4)
Totals	754	176 (23·0)	635 (84·5)	39 (5·2)	80 (11·0)	347 (46·0)	68 (9·1)	32 (4·3)	18 (2·4)	36 (4·8)	41 (5·5)	135 (18·0)	46 (6·1)

H+P=Hypertension associated with proteinuria H+O=Hypertension associated with oedema A.P.H.=Antepartum haemorrhage

(Percentage figures in brackets)

TABLE II

Methods of Delivery: Group (3): Postmature Women

	1957					1958				
	Total Number	No. of Cases of				Total Number	No. of Cases of			
		Oxytocin Drip	Spontaneous Delivery	Caesarean Section	Forceps Extraction		Oxytocin Drip	Spontaneous Delivery	Caesarean Section	Forceps Extraction
Primigravidae ..	150	29 (19·3)	133 (88·0)	4 (2·7)	13 (8·7)	144	23 (16·0)	113 (78·4)	9 (6·2)	22 (15·2)
Gravidae 2 and 3 ..	126	6 (4·0)	124 (99·0)	1 (0·9)	1 (0·9)	135	15 (11·0)	130 (95·5)	1 (0·7)	4 (2·9)
Gravidae 4 and 4+	59	10 (17·0)	59 (100·0)	0 –	0 –	66	10 (15·0)	63 (95·4)	1 (1·5)	2 (3·0)
Totals	335	45 (13·5)	316 (95·0)	5 (1·5)	14 (3·8)	345	48 (14·0)	306 (88·6)	11 (3·1)	28 (8·0)

(Percentage figures in brackets)

TABLE III

Induction of Labour 1957 and 1958: Group (4): Women Given an Oxytocin Drip

Total Number		Caesarean Section	Forceps Extraction	Hours from Induction to Drip		Hours from Drip to Delivery					Concentration of Drip			Days			
				24 and Less	25 and More	6 and Less	7 to 12	13 to 24	25 to 35	36+	½ Unit =1 to 2·5mU/min.	1 Unit =2 to 5 mU/min.	2 Units =4 to 10 mU/min.	1	2	3	4
Primigravidae	127	17 (13·0)	49 (39·0)	101 (79·0)	26 (21·0)	21 (17·0)	35 (28·0)	23 (18·0)	28 (22·0)	20 (16·0)	44 (35·0)	67 (53·0)	16 (13·0)	93 (73·0)	20 (16·0)	13 (10·0)	1 (0·8)
Gravidae 2 and 3	100	18 (18·0)	14 (14·0)	74 (74·0)	26 (26·0)	25 (25·0)	20 (20·0)	25 (25·0)	15 (15·0)	15 (15·0)	33 (33·0)	55 (55·0)	12 (12·0)	71 (71·0)	18 (18·0)	7 (7·0)	4 (4·0)
Gravidae 4 and 4+	68	6 (9·0)	3 (4·5)	57 (84·0)	11 (16·0)	20 (29·0)	15 (22·0)	12 (18·0)	10 (15·0)	11 (16·0)	21 (31·0)	41 (60·0)	6 (9·0)	50 (74·0)	11 (16·0)	5 (7·0)	2 (3·0)
Totals	295	41 (14·0)	66 (22·0)	232 (79·0)	63 (21·0)	66 (22·0)	70 (24·0)	60 (20·0)	53 (18·0)	46 (16·0)	98 (33·0)	163 (55·0)	34 (11·5)	214 (73·0)	49 (17·0)	25 (8·5)	7 (2·0)

(Percentage figures in brackets)

TABLE IV

Spontaneous Onset of Labour, 1958: Women Given an Oxytocin Drip

Total Number		Spontaneous Delivery	Caesarean Section	Forceps Extraction	Breech	Hours from Drip to Delivery					Concentration of Drip			Days Used			
						6 and Less	7 to 12	13 to 24	25 to 35	36+	½ Unit	1 Unit	2 Units	1	2	3	4
Primigravidae	61	23 (38·0)	12 (19·5)	23 (38·0)	3 (5·0)	18 (29·5)	20 (32·5)	6 (9·5)	6 (9·5)	11 (18·0)	30 (49·0)	27 (44·0)	4 (6·5)	48 (78·5)	9 (14·5)	3 (5·0)	1 (1·5)
Gravidae 2 and 3	33	24 (73·0)	4 (12·0)	2 (6·0)	3 (9·0)	12 (36·5)	10 (30·3)	3 (9·0)	4 (12·0)	4 (12·0)	18 (54·5)	12 (36·5)	3 (9·0)	27 (82·0)	5 (15·0)	1 (3·0)	– –
Gravidae 4 and 4+	16	14 (87·5)	1 (6·0)	– –	1 (6·0)	4 (25·0)	1 (6·0)	6 (37·5)	5 (31·0)	– –	5 (31·0)	11 (70·0)	– –	13 (81·5)	3 (18·5)	– –	– –
Totals	110	61 (55·5)	17 (15·5)	25 (23·0)	7 (6·0)	34 (31·0)	31 (28·0)	15 (13·5)	15 (13·5)	15 (13·5)	53 (48·0)	50 (45·5)	7 (6·0)	88 (80·0)	17 (15·5)	4 (3·5)	1 (1·0)

(Percentage figures in brackets)

TABLE V

(Percentage figures in brackets)

TABLE V

Weights of Babies in Groups (2), (3) and (4): 1957 and 1958

(Percentage figures in brackets)

	Total Numbers	10 Pounds+ (4·6 Kg.)	Between 9 and 10 Pounds (4·1 to 4·6 Kg.)	Between 8 and 9 Pounds (3·6 to 4·1 Kg.)	Between 7 and 8 Pounds (3·2 to 3·6 Kg.)	Between 6 and 7 Pounds (2·7 to 3·2 Kg.)	Between 5 and 6 Pounds (2·3 to 2·7 Kg.)	Between 4 and 5 Pounds (1·8 to 2·3 Kg.)	Between 3 and 4 Pounds (1·4 to 1·8 Kg.)
Group (2): Women 38 to 40 Weeks Pregnant									
Primigravidae ..	230	2 (0·9)	8 (3·5)	33 (14·3)	78 (34·0)	76 (33·0)	30 (13·0)	2 (0·9)	1 (0·4)
Gravidae 2 and 3 ..	307	3 (1·0)	11 (3·6)	58 (19·0)	99 (32·0)	96 (31·0)	34 (11·0)	5 (1·6)	1 (0·3)
Gravidae 4 and 4+	118	0 –	6 (5·1)	18 (15·0)	45 (38·0)	37 (31·0)	8 (7·0)	4 (3·4)	0 –
Group (3): Postmature Women									
Primigravidae ..	273	1 (0·4)	13 (4·8)	57 (21·0)	137 (50·0)	51 (19·0)	12 (4·4)	2 (0·7)	0 –
Gravidae 2 and 3 ..	241	5 (2·1)	19 (8·0)	61 (25·0)	88 (36·0)	57 (24·0)	10 (4·0)	1 (0·4)	0 –
Gravidae 4 and 4+	94	3 (3·2)	12 (13·0)	25 (27·0)	41 (42·5)	25 (27·0)	8 (8·5)	0 –	0 –
Group (4): Women Given an Oxytocin Drip									
Primigravidae ..	126	1 (0·8)	3 (2·4)	29 (23·0)	36 (29·0)	33 (26·0)	20 (16·0)	3 (2·4)	1 (0·8)
Gravidae 2 and 3 ..	100	1 (1·0)	5 (5·0)	10 (10·0)	27 (27·0)	47 (47·0)	10 (10·0)	0 –	0 –
Gravidae 4 and 4+	68	0 –	3 (4·4)	11 (16·2)	19 (28·0)	24 (35·3)	10 (15·0)	1 (1·5)	0 –

(In a number of cases (see text) the birth weight was not recorded and this accounts for the discrepancies between this Table and Tables I, II and III.)

(3) It will be seen from Table I that 23 per cent of the women in Group (2) were given an oxytocin drip whereas only 13·7 per cent of women in Group (3) required it (Table II). It is a very real concept that only about 20 per cent of all women fail to go into labour within a few hours of amniotomy, but that this percentage varies in different groups, and is often high in "toxaemic" patients. It is also obvious that the incidence of operative interference should be related to the total numbers induced, and not merely to those who were given a drip.

(4) The fact that 76·2 per cent of primigravid postmature women were delivered of babies weighing over 7 pounds, compared with 52·7 per cent in Group (2), 55·2 per cent in Group (4), and a hospital incidence of 51 per cent (Table V) affords positive evidence of the reality of postmaturity. I regret that many of the induction cards omitted to state the weight of the baby. Seeing that this omission is dependent on the random behaviour of the house surgeon, it cannot affect the argument. In any case the infant weight was left out in only 7 per cent of the primigravidae in Group (3), and the hospital incidence was based on the weights of 300 babies taken from consecutive charts recording single pregnancies in primigravidae. If any hospital can show that they have delivered 680 women 42 weeks or more pregnant, without inducing labour and without performing more than 2·3 per cent of Caesarean sections, and sent all but five home with living babies, I will consider giving up induction of labour because of postmaturity.

(5) Induction of labour is perfectly safe for the mother if performed *secundem artem*. Only one mother, out of nearly 3,500 in whom labour was induced, has died during the past seven years, and the death was due to air embolism and was in no way related to induction of labour.

(6) The term "ripe cervix" is a horticultural term used in an almost riparian setting. I use it to denote that the cervix is reasonably soft, will easily admit one finger, and is not more than an inch long. On the one hand I would not willingly perform amniotomy if the cervix is long and hard and barely admits a finger, while on the other it is fairly obvious that if the cervix is completely effaced, is very soft, and will admit two fingers, the obstetrician will have to act fast to prevent the woman going into spontaneous labour. In my experience it is always safe to induce labour in a multigravida, whatever the state of the cervix, providing she has given birth to a child within the previous three years. A multigravida who has not given birth to a child for 10 years should, I suggest, be regarded as a primigravida. The state of the cervix is not often a factor which causes us to postpone amniotomy.

I have for nearly ten years maintained that intact membranes are the greatest single hindrance to normal labour, and this view is gaining clinical acceptance and scientific support (Calkins, 1952; Embrey, 1953; Bainbridge *et al.*, 1958; Cibils *et al.*, 1959). It is, therefore, sound practice to rupture the membranes and nobody has ever been born until they have ruptured or been ruptured. The Caesarean section rate for the hospital was 3·6 per cent, and for the city less than 2 per cent.

It is fitting to observe that weekly antenatal care, made possible by an increase in the number of antenatal at the expense of lying-in beds and frequent resort to induction of labour, together with the outstanding co-operation of the Local Health Authority and the general practitioners, have virtually abolished eclampsia and pre-eclampsia from the City of Bradford. We have not had a death in the city from eclampsia of either mother or child for 5 years, and during the past 7 years there has been only one maternal death associated with any form of toxaemia or even with hypertension. The corrected perinatal mortality associated with all forms of hypertension (140/90 mm. Hg and over) was 3·6 per cent, and that for all patients with hypertension including those with associated proteinuria and/or oedema, whether booked or unbooked, was 5 per cent. The incidence of prolonged labour (over 48 hours) was 25 in 4,300 booked patients, or 0·6 per cent. Large numbers of "European workers" and unhealthy immigrants from the Commonwealth, moreover, work in the city.

The face of midwifery has changed, and is changing. Procedures which were right in 1940 would not have been right in 1910, and sound practice today may not be acceptable in 1970.

It is essential to avoid rigidity in thought, whether as individuals, colleges or corporations, and it is most desirable that different patterns of procedure should be tried in different centres until the perfect system is evolved and finality is achieved. I believe it to be desirable for the present to do 100 inductions of labour if thereby 2 babies can be saved or 4 Caesarean sections avoided. I am nevertheless fully convinced that when slums and evil housing conditions have been abolished, smoke has ceased to poison our atmosphere, the elementary laws of dietetics have been put into practice, married women have ceased to work in factories, and the ordinary man in the street has become litter conscious—that both induction of labour and Caesarean section will have fallen into desuetude. Finally, two sobering thoughts: (1) that we as obstetricians are to no little extent responsible for the alarming world increase in population, and (2) that whereas we strive to decrease the perinatal mortality by one per cent the women of England and of the United States of America deliberately destroy approximately 10 per cent of the foetuses which are formed.

I express my thanks to my colleagues, Mr. G. A. Craig and Mr. A. C. Muir for their share in the results reported, and our Senior Registrar, Miss J. M. B. Muirhead (now at Leeds) for volunteering to extract the figures for 1958.

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PROFESSOR H. M. CAREY (Auckland)

Posterior Pituitary Oxytocin

Intramuscular pitocin is frequently ineffective and potentially dangerous. Among the points to be noted may be mentioned:

(1) Uterine tone is raised for 10 to 15 minutes in a proportion of cases with doses of 2·5 units, leading to temporary slowing of the foetal heart rate.

(2) Accidental intravenous injection or rapid absorption can occur, producing prolonged tetanic contractions.

(3) The wrong dose is sometimes given when administration is left to junior nurses.

(4) Administration every 20 to 30 minutes means that the effect of the second injection is superimposed on the second half of the first injection, for the action of a single dose lasts for up to an hour.

(5) Some patients are very sensitive to the action of posterior pituitary oxytocin, others are relatively insensitive.

(6) It is irrational to suspend injections when the contractions become painful, and one must remember that painless contractions can produce foetal distress.

Intravenous pitocin is more efficient and safer than intramuscular administration; it increases the quantity but not the quality of uterine activity. Certain precautions are necessary and the following points are to be noted:

(1) An excessive drip rate, especially at the start, must be avoided.

(2) Some patients are hypersensitive and the initial contractions may be prolonged.

(3) With 2·5 units of pitocin in 500 ml. 5 per cent glucose in water, one should start with a drip rate of 5 drops per minute and increase the rate by 5 drops per minute every 10 minutes, until uterine contractions occur every 2½ to 3 minutes.

(4) A regulator that allows fine control of the drip rate should be used or a mechanical pump that will always deliver the number of drops per minute at which the drip rate regulator is set.

(5) A close watch on the foetal heart must be

kept. A vibration pick-up strapped to the mother's abdomen allows the foetal heart to be heard through a loud-speaker and makes possible the very early detection of any fluctuations.

(6) Before labour is established, the patient's subjective appreciation of the duration and frequency of contractions is unreliable. The uterine response to pitocin infusion must be recorded by placing a hand over the fundus and palpating each contraction. Alternatively, a tocograph which will record the frequency and duration of contractions and the uterine tone between contractions should be used. External tocographs are not very comfortable for the patient and they do not measure the uterine tone with any degree of accuracy; the record of the amplitude of the contractions is also unreliable. A polythene catheter introduced through the cervix into the amniotic cavity at the time the membranes are ruptured is the best and most accurate method of recording uterine activity. It is comfortable and well tolerated by the patient, and it allows the introduction of antibiotics into the amniotic cavity.

Amongst the *causes of failure* of the pitocin drip may be listed:

(1) Intact membranes: oxytocin drips are less effective when the membranes are intact.

(2) Inadequate drip rate: due to the wide range of sensitivity, some patients require a high dose of pitocin. The drip rate should be increased until a contraction occurs every 2½ to 3 minutes. The amplitude of the contractions is not a good guide to oxytocin requirements.

(3) Period of administration too short: sometimes the drip has to run for 8 to 16 hours before the cervix starts to dilate.

(4) Marked degrees of inco-ordinate uterine activity: pitocin only increases the quantity and not the quality of uterine activity. If the degree of inco-ordination is not very great, increasing the quantity may compensate for the poor quality. Normally, the duration of a contraction is very constant and is largely independent of the amplitude. Marked degrees of inco-ordinate uterine activity are rare but minor degrees are common, especially with first labours.

(5) True cervical rigidity: very occasionally the cervix fails to dilate even with adequate and well-co-ordinated uterine activity over a considerable period of time and despite descent of the head well into the pelvis.

(6) Mechanical difficulties: an unsuspected large baby in a first labour may reduce the efficiency of the uterine contractions.

Relaxin and Pitocin: Relaxin softens connective tissue and facilitates cervical dilatation provided uterine activity is adequate and well-co-ordinated. Preliminary observations suggest that if a high level of uterine activity is produced by pitocin, the administration of fairly large doses of relaxin over a period of time will shorten the duration of the first stage of labour.

Indications for the Use of Intravenous Pitocin: The commonest indication is the induction of labour following artificial rupture of the membranes: about 40 per cent of primigravidae and 20 per cent of multiparae are not in labour within 24 hours of amniotomy. Within the next 2 days all but 3 per cent of the patients given an oxytocin drip will be delivered or well-established in labour.

Ergot Oxytocics

Ergometrine and dihydroergotamine (DHE) are qualitatively similar. Small doses, e.g., 0·25 mg. DHE, increase the frequency of uterine contractions without alteration of the amplitude. Larger doses, e.g., 1 mg. DHE, increase uterine tone without loss of co-ordination. Clinically, weight for weight DHE is one-twentieth as active as ergometrine, but it has a latency of 45 to 60 minutes and a duration of action of 9 to 12 hours following subcutaneous injection. Administered in the same way, ergometrine has a latency of 3 to 5 minutes and a duration of action of 3 to 4 hours. The action of DHE is the same on both normal and inco-ordinate uterine action. In the presence of a living foetus the dose of DHE should not exceed 0·25 mg. every 8 hours, but its use is best avoided as intravenous pitocin is more effective and safer.

(This paper was illustrated by a film.)

MR. M. P. EMBREY (Oxford)

A CRITERION OF OXYTOCIC ACTIVITY

BECAUSE of species difference in drug response the results of laboratory experiment cannot always be translated to clinical practice. I believe it is essential that any new compound with alleged oxytocic activity should be submitted to objective tocographic assessment before being used in clinical obstetrics.

The need for this advice has been exemplified several times in the history of ergot. Thirty years ago it was thought that ergotoxine and ergotamine were the essential substances in crude ergot (Clark, 1927); but, despite their potency in the laboratory, the alkaloids were disappointing in practice and much slower in action than crude Extr. Ergot Liq. (Moir, 1932). With the discovery of ergometrine (Moir, 1932; Dudley and Moir, 1935) the reverse obtained. The standard preparations of isolated guinea-pig and rat uterus used for the assay were not reliable (Bovet-Nitti, 1952), so, in the laboratory, ergometrine was disappointing yet, clinically, it was found to be the most powerful oxytocic of all.

The need for a stringent test of oxytocic activity has recently been re-emphasized by studies I carried out with W. J. Garrett. The first of these investigations concerned the fairly recent semi-synthetic ergot alkaloid, dihydroergotamine. This was claimed (Sauter, 1948; Gill and Farrar, 1951) to have no direct oxytocic action, yet was thought to possess strong sympatholytic properties. But Garrett (1955) found that dihydroergotamine does not modify either the stimulant effect of noradrenaline or the inhibitory effect of adrenaline on the parturient uterus; and subsequently (Embrey and Garrett, 1955), we were able to demonstrate tocographically in the puerperal uterus the undoubted oxytocic action of the drug (Fig. 1) —an action very like that of ergotamine and ergotoxine.

Comparable results were later obtained with Hydergine, which is a mixture of the dihydro derivatives of ergotoxine, ergocryptine and ergocristine (Garrett and Embrey, 1955). Garrett and I found that each of these alkaloids, and the parent mixture, possessed direct oxytocic activity when tested on the human puerperal uterus (Fig. 1).

In the case of another new synthetic ergot-like derivative, Tochergamine, our experience was quite the reverse (Garrett and Embrey, 1958). This compound, prepared and studied by Bovet-Nitti (1952) in the laboratory, has been found to exhibit oxytocic activity equal to that of ergometrine in experimental animals. Garrett and I tested Tochergamine on the intact human uterus and found it to be without demonstrable oxytocic action in doses of 1–20 mg. parenterally, i.e., more than three times the recommended dose.

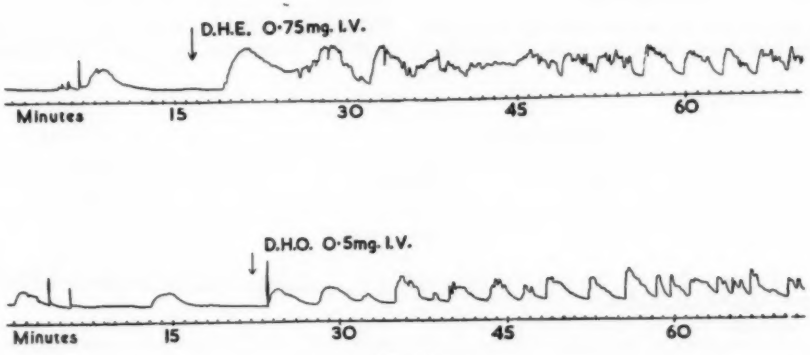

FIG. 1

The oxytocic effect of dihydroergotamine and dihydroergotoxine. (Puerperal uterus.)

The Ergometrine Drip

I believe that there can never be any place for the use of an intravenous ergometrine infusion with a live child *in utero*. But in cases of abortion or intra-uterine death it could conceivably have some merit and I have employed the method now on a few occasions. It is my impression that it is not possible to equate an ergometrine drip with an oxytocin infusion because there is a fundamental qualitative difference between the two, namely, the dangerous spasm-producing properties of ergometrine.

While a single injection of a large dose of oxytocin can produce tetanic uterine contractions, the spasm is short-lived compared with that of ergometrine. So it is found tocographically that, given in the commonly recommended dosage, spasm is not usually evident with an oxytocin drip and the uterus relaxes well between contractions; in any event, spasm can readily be controlled by stopping the drip. But with an ergometrine drip (Fig. 2) any attempt to augment uterine activity by increasing the infusion rate leads to a dangerous element of hypertonus and an inco-ordinate or fibrillated contractility pattern, lacking diastolic relaxation; moreover, the uterine hypertonus persists long after the infusion is stopped.

The Actions of Synthetic Vasopressin and Synthetic Oxytocin on Uterine Contractility

It is now some 30 years since the posterior pituitary hormone, by a process of chemical fractionation (Dudley, 1923; Kamm *et al.*, 1928) was first persuaded to yield its two active principles, vasopressin and oxytocin. What is perhaps not generally appreciated is that in the commercially available products, Pitressin and Pitocin, the differentiation is incomplete so that each contains approximately 10 per cent of the other. I mention this because it might explain the doubts that have been raised from time to time regarding the specificity of action of the two fractions, the paradox of the undoubted oxytocic effect which Pitressin shows at least on occasion, and the conflicting results reported from animal, *in vitro* and clinical experiments (Bourne and Burn, 1928; Robson, 1933; Adair and Haugen, 1939; Russell, 1943).

Thus, in the case of the human pregnant uterus, Moir (1944) found that in early pregnancy vasopressin actually produced a greater oxytocic response than oxytocin itself, whereas in late pregnancy, labour and the puerperium, the position was reversed and oxytocin the more powerful drug. More recently Schild, Fitzpatrick and Nixon (1951) have repeated some of this work with slightly different results. They found that in the first trimester vasopressin was about equiactive with oxytocin, while in the second trimester vasopressin was about 1½ times as active as oxytocin.

The brilliant researches of Du Vigneaud and his colleagues (1953, 1954) have in recent years provided us with synthetic oxytocin, which in clinical practice appears identical with its natural counterpart (Bainbridge *et al.*, 1956; Francis and Francis, 1956). Now Du Vigneaud and his associates have also synthesized the

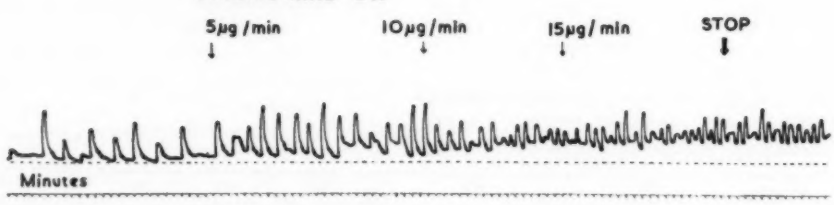

Fig. 2

Intravenous ergometrine infusion. Increasing the drip rate leads to dangerous hypertonus.

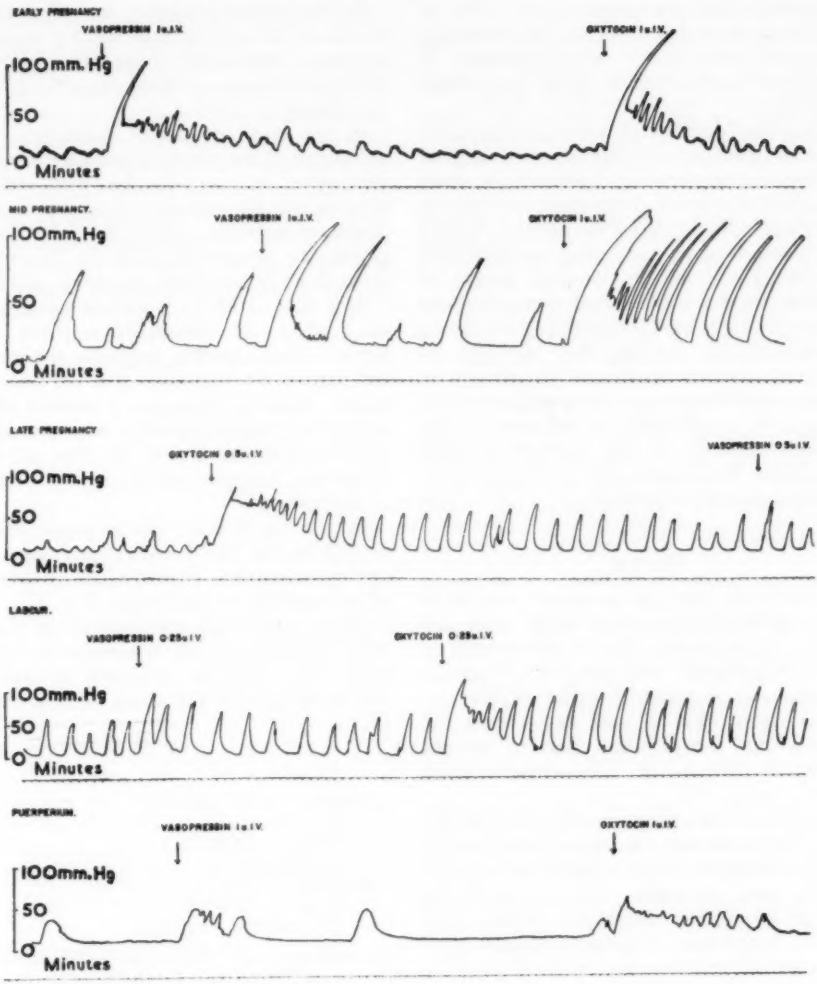

FIG. 3

The comparative effects of vasopressin and oxytocin in early, mid and late pregnancy, labour and the puerperium.

vasopressor hormone (Du Vigneaud, Lawler and Popenoe, 1953; Du Vigneaud, Gish and Katsoyannis, 1954; Bartlett *et al.*, 1956), and I have had the opportunity of testing synthetic vasopressin and comparing its effect on uterine contractility with that of synthetic oxytocin.

Trials were carried out in early, mid and late pregnancy, in labour and the puerperium. In

each patient, objective records of the effect of equal intravenous doses* of the two hormones on uterine contractility were obtained by internal or external means, using the Oxford tocograph.

Taking the "duration of action"—that is, the time until the tocograph returns to its original base line—as the measure of response, a direct comparison of the two drugs could be made in each instance. Now, because the uterine response to an oxytocic varies according to individual susceptibility and the physiological activity of the organ, there is a difficulty in comparing one case with another; but by introducing a common denominator and relating the "duration of action" of oxytocin to that of vasopressin in arbitrary units in each case, an assay between the two oxytocic drugs could be formulated with increasing accuracy as the number of cases accumulated. The results of a small series have been encouragingly consistent.

Results

As with the natural products, the effect of the synthetic hormones varies with the duration of pregnancy. But it can be said at once, that synthetic vasopressin is, at least on occasion, a quite powerful direct oxytocic in its own right. This at least disposes of the allegation that the oxytocic effect of the old Pitressin is due to its contamination with Pitocin.

In the first trimester of pregnancy, I found that the oxytocic response to vasopressin—especially when the uterus is physiologically active—is a powerful one. Oxytocin, too, is an active stimulant of uterine contractility at this time (Fig. 3). Sometimes vasopressin actually produces a greater response than oxytocin; in other cases oxytocin is the more active drug. By the method of assay outlined, vasopressin is found to be equiactive or a little more than equiactive with oxytocin.

In the second trimester, the effect of vasopressin is still well marked but the response to oxytocin is appreciably greater (Fig. 3). Oxytocin now possesses two or three times the activity of vasopressin.

In the later months of pregnancy, as the behaviour of the uterus gradually changes, the superiority of oxytocin becomes still more obvious and as term approaches it is clearly the dominant oxytocic, possessing 5–10 times the activity of vasopressin (Fig. 3). The effect of vasopressin is now often transient or feeble.

This state of affairs is maintained in parturition, when the contractile response of the uterine musculature to oxytocin is spectacular and always far surpasses that of vasopressin; indeed, vasopressin is almost without effect or sometimes merely augments an expected spontaneous contraction (Fig. 3). The activity of oxytocin in labour is assayed at 10–15 times that of vasopressin.

In the puerperium the oxytocic responses evoked by the two hormones are very similar to those seen in labour; and again the superiority of oxytocin is overwhelming (Fig. 3).

These results are summarized in Figure 4 which diagrammatically represents the changing ratio of the "duration of action" of oxytocin to that of vasopressin and which visually interprets

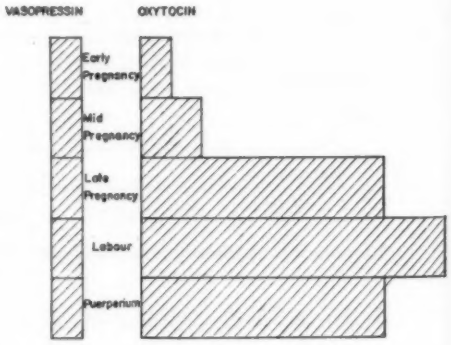

Fig. 4

Diagrammatic representation of the "duration of action" of vasopressin and oxytocin in early, mid and late pregnancy, labour and the puerperium.

* The doses used in each patient were equal when reckoned "unit" for "unit". It must be understood, however, that the "unit" of vasopressin refers to its pressor activity and the "unit" of oxytocin to its oxytocic activity. The two units of measurement are, therefore, quite unrelated.

the mounting activity of oxytocin compared with vasopressin as term approaches.*

Alternatively—and perhaps more correctly—the effects of vasopressin and oxytocin can be compared by studying their "relative difference" of action. This method of representation is seen in Figure 5. Here again the two hormones are seen to be almost equiactive—with a slight bias in favour of vasopressin—in early pregnancy; but as pregnancy advances the superiority of oxytocin becomes increasingly striking and near term, in labour and in the early puerperium, is overwhelming.

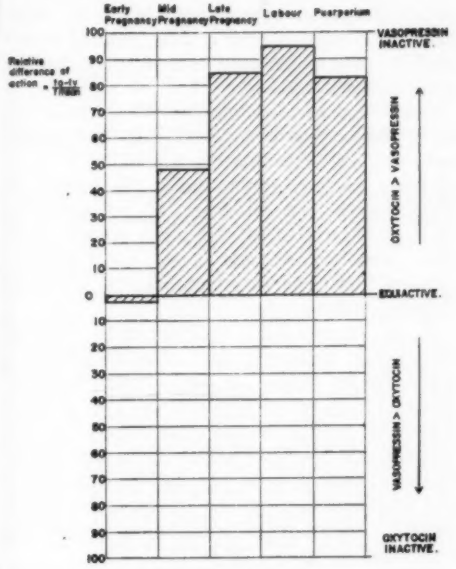

FIG. 5

The "relative difference" of action of vasopressin and oxytocin in early, mid and late pregnancy, labour and the puerperium.

* An objection to this method of representation is that in a few cases it is difficult to be sure if vasopressin has had any effect, so that the ratio "duration of action" (oxytocin)/"duration of action" (vasopressin) approaches infinity. This difficulty is overcome by calculating the "relative difference" of action: $\frac{to-tv}{t\ mean}$ i.e. $\frac{to-tv}{(to+tv)/2}$

where to = duration of action (oxytocin)
and tv = duration of action (vasopressin)

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DR. DAVID E. WARDEN

(Long Island, New York)

DURING the past twenty years our habits and attitudes regarding the induction of labour have undergone radical change. Indeed, for many years prior to Theobald's report in 1948, the literature contains many references to the use of bags and bougies, to castor oil and quinine, to

subcutaneous and intramuscular pitocin, even to the use of powdered ergot! The capricious action and sometimes traumatic results of the use of these preparations is attested to by the variety of agents then in use. With the publication of Theobald's paper in 1948, a new phase in the study of induction of labour began, with the introduction of the dilute intravenous pituitrin infusion. In the past ten years a great deal of controversy has centred around the question of the safety of this method. It is indeed very easy and very human to criticize the tool when, in fact, the fault may lie with the man behind the tool. Some of this hostile attitude, no doubt, has developed because of the unfavourable results with older methods, some through lack of experience and carelessness. If accidents are to be prevented, supervision of patients undergoing induction cannot be delegated to medical students and nurses.

Recently I have had the opportunity to study the induction and stimulation of labour by means of dilute intravenous oxytocins in a 200-bed suburban general hospital whose obstetrical-gynaecological staff consists for the most part of qualified specialists or general practitioners with extensive experience in obstetrics. This is precisely the type of institution in which the great majority of births in our country occur.

During the two years 1957 and 1958 there were 277 inductions or stimulations using this method in 4,880 deliveries, an incidence of 7·3 per cent. Somewhat more than half the procedures were for the purpose of induction and the vast majority of patients were multiparae. There were no maternal deaths; there were no foetal deaths or injuries attributable to the method; and there were no instances of ruptured uteri. There were no prolonged labours and the necessity to repeat the drip at a future time occurred in only 13 instances. Accidental prematurity occurred not once. Our only cause for concern had been the somewhat increased incidence of post-partum haemorrhage. In the earlier years of induction with intravenous oxytocin at our hospital, the infusion was ordinarily started prior to artificial rupture of the membranes. Our present method of elective induction in most cases is to admit the patient at or near term provided the cervix is 2 cm. or more dilated, at least half effaced and the presenting part not higher than "station minus one". Vaginal examination is carried out and the membranes ruptured. If labour has not supervened within several hours, the drip is started, very slowly at first, and is only rarely ineffective. (Our usual solution contains one unit of oxytocin per 100 ml. of 5 per cent glucose in water.) When delivery prior to term is indicated in toxaemia, diabetes or Rh iso-immunization, it may be necessary to "prime" the cervix by means of the drip on more than one occasion or to employ caudal anaesthesia or paravertebral lumbar sympathetic block to make the cervix more receptive. The method is not used in cases of previous section or to test the adequacy of the pelvis.

Aside from elective induction for convenience, the technique may be especially useful in certain instances of: (1) uterine inertia; (2) long-standing ruptured membranes; (3) premature separation of the placenta; (4) postmaturity; (5) intra-uterine death including missed abortion; and (6) selected cases of toxaemia, diabetes and Rh iso-immunization requiring delivery prior to term.

Based on the facts in this study and the impressions gained in our experience with a much larger group of cases over the past decade, the method appears to be safe. A basic ingredient of the success and safety of this technique is common sense. If the indications and contra-indications are strictly understood and respected and if the obstetrician is well trained, competent and present, the method has a substantial margin of safety.

Dr. J. R. Saunders (London)

May I apologize on behalf of Professor Nixon and Dr. Norman Smythe who are both unable to be here and may I in their stead very humbly say a little about Dr. Smythe's oxytocin sensitivity test? Most obstetricians are now familiar with the test; very briefly, a small dose of either syntocinon or pitocin is given intravenously and contractions recorded on the tocograph, the dose being 0·01 of a unit every minute until the

uterus contracts. The majority of patients who are sensitive to 0·01, 0·02 or 0·03 of a unit will be in labour within 24 hours; with those who are less sensitive, responding to 0·04 of a unit, labour may not start for a day or two after amniotomy. A final group, even more insensitive showing no contraction with 0·05 of a unit, may be infused with syntocinon not to induce labour but in an attempt to ripen the cervix and to improve the irritability or sensitivity of the uterus.

Finally, if Professor Nixon were here I am sure he would urge that syntocinon or pitocin infusion is both a safe and a proper procedure when properly used.

Mr. D. J. MacRae (London)

Monitoring the Foetal Heart During a Pitocin Drip (with film)

I have come to show a short film on monitoring the foetal heart during a pitocin drip, but I should first like to make some general observations on the subject.

Intravenous pitocin has, I find, obviated the need for hysterotomy in cases of hydatidiform mole and has expedited the difficult induction and delivery, after the 12th week of pregnancy, of cases of missed abortion. This is one of the most important advances in recent obstetric practice. It is unfortunate, however, that the careful technique and low concentration advocated by Mr. Theobald for the induction of labour is not generally followed; and it seems that the accompanying glucose bottle, which I recommended at the Leeds Congress (MacRae, 1952), now contains pethidine, in anticipation of uterine spasm and foetal distress.

When a pitocin drip is used for the induction of labour, it is necessary to keep a more careful watch on the foetus. This can be done by the cardiophone.

As will be seen from the film the patient is saved the considerable inconvenience and anxiety associated with repeated auscultation of the foetal heart and is able, if she wishes, to rest comfortably on her side. The cardiophone will keep a continuous check on the foetal heart rate and rhythm; the uterine contractions can be recognized, and their frequency and their effect on the heart action noted; heard also are the reflex kicks of the foetus or the tumultuous movements of distress.

These observations can be made in the Sister's Office while other work is being carried out and, if labour is established, they can be made automatically at regular intervals either by sound, or dynographic tracings, or tape recordings. If complete quiet is desired it is also possible to listen through the cardiophone by ear-phones. I have, incidentally, found the cardiophone of particular value, as reported in the *Lancet* (MacRae, 1959), in cases of trial labour where a sleeping drug has been given, and during the second stage of labour when foetal heart irregularity is common and treatment urgent.

I must confess, however, that I seldom have occasion to use a pitocin drip, and I give prophylactic ergometrine only when indicated and not as a routine in labour. I wonder, finally, if we should not continue with our endeavour to avoid unnecessary drugs and interference and give more patients the lasting joy and satisfaction of having their babies by their own unaided efforts.

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Professor Antoine (Vienna)

I speak as a defender of the oxytocic drugs. In doing so, I may be justified by the fact that I have been using oxytocic drugs for more than 35 years, since the time when there did not exist an international unit. There is one strange thing with the oxytocics. If a patient who has any accident during labour has had any amount of oxytocic, the oxytocic is blamed for the trouble which has arisen. What would you say if a surgeon at laparotomy cut by chance the common iliac artery? Would it be the fault of the knife? And so it is with the oxytocics. I think it is wrong to talk about dangerous and non-dangerous oxytocics. I believe we should

always say effective and non-effective oxytocics, just as we talk about other drugs. Most of the effective drugs—the morphine group, digitalis and many others—are potentially dangerous. If something happens during delivery due to the fact that an oxytocin has been given, it is because the doctor not the oxytocin was dangerous.

Dr. R. R. Trussell (Kampala, Uganda)

Several members have spoken this afternoon of the doctor and his administration of oxytocin. In Uganda we encounter the administration of oxytocin by the patient herself. I suppose most parts of the world have their own traditions of local medicine taken to make labour easier; that is particularly true of African patients. We think that possibly 90 per cent of them take some decoction or other in water or alcohol soluble form, and we feel that our figure of 173 ruptured uteri in the last 15,000 deliveries is contributed to by this oxytocic factor. The pattern of these ruptured uteri, occurring as they do, a very few in first deliveries, quite an appreciable number in second or third deliveries, after a comparatively short duration of labour, leads us to believe that there may be some active factor in action. We cannot say more than that at the moment. The obvious step is to investigate this substance they take and this is being done at the moment with great difficulty. Information was obtained about a certain bark from a midwife working in a mission hospital. She was very loath to give the exact tree, but the Physiology Department took over; the difficulty was not to find the tree, but to find any bark on it. This work will be reported in full by the Department of Physiology, but I believe they have reached the stage of producing a pure crystalline substance. Just before I came on leave, I saw this acting with a tocograph on the uterus of a pregnant Rhesus monkey. There seemed to be no doubt that it had an oxytocic action, and so far its toxic effects appear to be small. It may, of course, be chemically identical with substances we already use, but it is just possible that we might have here another oxytocic agent.

Dr. Duncan Reid (Boston)

Since its re-introduction some two decades ago, pituitrin in some form has become accepted as a useful therapeutic agent in the treatment of prolonged labour. In our clinic, beginning in 1938 with the advent of X-ray pelvimetry which permitted the clinician an accurate means of establishing the cephalopelvic relationship, pituitrin has been administered for the prevention and definitive treatment of functional dystocia and resultant prolonged labour. In 1946, a series of some 1,600 patients receiving pituitrin in the course of first and second stage labour was reported, from which certain conclusions and criteria were gathered regarding the use of this powerful oxytocic agent. In addition to its potential dangers came the realization that the drug had definite limitations. Since then it has been shown repeatedly that pituitrin, although useful, fails to produce the desired results in at least 10–20 per cent of the cases. This is to say, the uterus is or may become refractory to the drug and progress in labour fails to occur or there is failure to induce labour.

In the management of prolonged labour (which unquestionably is a sound indication for the use of this drug) according to our policy pitocin in some form is administered by the 18th hour, and no later than between the 24th to the 36th hour, with the expectation that pelvic delivery will occur before the 40th hour. In most cases within 3 to 4 hours from the time of the initial administration of pituitrin the cervix will become completely dilated and the patient deliverable by either a normal mechanism or low forceps. If no appreciable progress is noted after this time, however, it is assumed that the drug is not likely to produce the desired results. Actually, it is believed that further administration of the drug and postponement of delivery may only increase the hazard of irreversible anoxic damage to the foetus. This policy has reduced the incidence of prolonged labour to 1·4 per cent and the foetal mortality from 11·7 per cent in a previous series from the same clinic to 5·4 per cent. Goodwin's study (in preparation) will also report that the overall morbidity rate in the babies was 20·5 per cent,

but among primiparous patients over 30 years of age it was 39·7 per cent or nearly double. One must question the wisdom of subjecting women in this age group having their first baby to a labour beyond 18–20 hours' duration.

Regardless of its mode of administration, the dangers of pituitrin therapy in the first and second stages of labour must not be minimized. Tetanic contractions may follow minute doses of the agent even one-half minim or less intramuscularly or 10 drops per minute by the infusion method. Slowing of the foetal heart tones below 100 beats per minute for a 5- to 10-minute interval is not without its hazards to the foetus. The weakness of all the papers up to the present concerned with pitocin administration prior to the 3rd stage of labour, is the fact that there has been no follow-up of the babies born to the mothers who have received the drug. Its wholesale use in obstetrics, generally without sound indication, particularly in the United States, deserves comment. Reference is made specifically to pituitrin being used in some form to induce labour electively or to shorten a normal labour. The experience of our Maternal Mortality Committee of Massachusetts and in other States lends support to Mr. Wrigley's views.

MR. A. J. WRIGLEY (London) (*Summing Up*)

NEARLY everybody here is familiar with the tremendous amount of work that Professor Chassar Moir has done in trying to put before us a true picture of the action of these drugs. I must say in self-defence, with reference to Professor Antoine, that it is exactly 35 years since I, if you like to use the word, experimented with the subcutaneous (as it was then) injection of pituitrin. I remember very well using a Y tube—it had to be double to allow quick enough absorption. It was given up after a time because of timidity, I suppose it would be called now, on my part. I am sure this discussion has helped. I may have been a little provocative but I am entirely sincere in my belief in the dangers of repeated intramuscular injections. We have to remember that in this country childbirth is now enormously safe, and we must think very carefully about anything that can possibly make that safety less.

GENERAL NOTES

Local Committee

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Congress Secretary:	Miss J. Ayres.

Social Events

Tuesday, 14th July:	Reception in the evening in the National Museum of Wales by invitation of the President of the Congress and Mrs. Strachan.
Wednesday, 15th July:	Reception in the evening at University College by invitation of the University College of South Wales and Monmouthshire and the Welsh National School of Medicine.
Thursday, 16th July:	Garden Party in the afternoon in the grounds of Cardiff Castle by invitation of the Lord Mayor. Congress Banquet in the evening in the City Hall.

ACKNOWLEDGMENT

The Editor of the *Journal* is greatly indebted to Dr. J. G. Lawson, the Local Editor, for the care with which he has prepared the Proceedings of the Congress for publication.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

AT the Meeting of Council held in the College House on Friday, 16th October, 1959, with the President, Professor A. M. Claye, in the Chair.

The following were admitted to the **Membership:**

Robert Marshall Adam.
Margaret Aureol Austin.
Debabrata Bhattacharyya.
Sridevi Biswas.
Basil Bloch.
Audrey Anne Boutwood.
Michael David Cameron.
Aseem Prakash Chakravorty.
Srinivas Krishnama Char.
David Charles.
Sunil Kumar Chaudhuri.
Ellis Cooper.
John Daniel Crowley.
Ian James Dalrymple.
Kaushlya Dodeja.
David Anthony Stirling Eddie.
Edwin John Esler.
Jill Margaret Evans.
William Dennis Fraser.
Srasht Kumari Ghai.
Aloka Gupta.
John Desmond Hehir.
Alexander Herriot.
Beverley John Herbert Insull.
Chelliah Kathirkamanathan.
Tye-Hin Lean.
Sydney Lubert.
Rodney Hugh Lumer.
Ronald Robert Macdonald.
Kathleen McKee.
Hugo McVey.
Sanat Kumar Mandal.
Alastair William Maxwell.
Cecil Dermot Moloney.
Kamala Mukherjee.
Margaret Helen Murray.
Christopher James Barrington Orr.
Olga Mavis Rampersaud.
John Adolf Riedel.
John Gow Robertson.
Martin Lyle Robinson.
David William Acton Rodwell.
Nagendra Nath Roy Chowdhury.
Clifton John Ryan.
John Monteith Samson.
Stanley Albert Seligman.
Nigel Gordon Steere.
Doreen Patricia Grieve Stewart.
Roy Harding Syred.
John Heywood Taylor.
Gytha Wade.
Pearl Allan Walker.
Jayaweera Bandara Wedande.
Charles Richard Whitfield.
Arthur Claude Wilson.

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L. FARRER-BROWN,

Director of the Nuffield Foundation

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Proper scientific names giving both genus and species should be italicized, with an initial capital and contraction for the genus only after a full spelling at the first mention, thus:

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Each sentence should have its proper components thus:

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Dates should be given as 10th May, 1946, and *not* 10.V.46. Numbers should be in the form of numerals and not words except when beginning a sentence, thus "Fifteen patients out of a total of 60 exhibited," etc. The official rather than the proprietary names of drugs must be used. The Journal convention is gr. for grains; g. for grammes; Kg.; ml. (*not* c.c. or c.cm.); mg.; pounds (*not* lb.); ounces (*not* oz.), etc., and wherever suitable the metric equivalent of an English measure should be given, for example, when recording pelvic measurements, size and weight of babies, tumours, etc.

When comparable figures are given, either the English or the metric mode must be followed, thus: the excretion of urine/24 hours should be shown in ml. (and not ounces) when the urinary or blood-urea is given in g./100 ml.

REFERENCES

In the text the author's name should be given, with the date of publication and the list of authors quoted put at the end of the text in alphabetical order as in the Harvard Scheme: Author's name, initials, year of publication (in brackets), name of journal (*italics* abbreviated), volume number (underlined) and page number. In the case of books the order is: Author's name, initials, year of publication, full title (*italics*), edition, publisher and place of publication, page, thus:

Brown, H. E., and Jones, B. K. (1943): *J. Obstet. Gynaec. Brit. Emp.*, **2**, 128.

Sampson, P. (1940): *Obstetrics for Midwives*. 2nd edition. Fraser, London. p. 9.

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